
# ENCYCLOPEDIA OF Gastroenterology

EDITOR-IN-CHIEF

Leonard R. Johnson

Volume 3

O–Z

Index

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# EDITORIAL BOARD

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**Leonard R. Johnson**

*University of Tennessee*

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ELSEVIER
ACADEMIC
PRESS

Amsterdam Boston Heidelberg London New York Oxford
Paris San Diego San Francisco Singapore Sydney Tokyo

This book is printed on acid-free paper.



Academic Press
*An imprint of Elsevier*
525 B Street, Suite 1900, San Diego, California 92101-4495, USA
http://www.elsevier.com

Elsevier Ltd.
The Boulevard, Langford Lane, Kidlington, Oxford, OX5 1GB, UK
http://www.elsevier.com

Library of Congress Catalog Card Number: 2003109370

International Standard Book Number: 0-12-386860-2 (set)
International Standard Book Number: 0-12-386861-0 (Volume 1)
International Standard Book Number: 0-12-386862-9 (Volume 2)
International Standard Book Number: 0-12-386863-7 (Volume 3)

Printed in the United States of America
03 04 05 06 08 MM 9 8 7 6 5 4 3 2 1

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# FOREWORD

People of my age often have mixed emotions about encyclopedias, probably because they conjure up memories of writing high-school term papers and reading from 26-volume encyclopedias in the library. Those individuals who came of age in the computer era may not fully understand to what I am referring. As I have grown older, I have rediscovered the usefulness of encyclopedias, especially those comprising only 1, 2, or 3 volumes. My favorite for general knowledge is the *Columbia Encyclopedia*, which was first published in 1935 and is now in its fifth edition. I have used this encyclopedia on many occasions. For example, while developing a Grand Rounds lecture on celiac disease, I discovered that the disease was described exceedingly well in the second century A.D. by Aretaeus the Cappadocian. Where is Cappadocia? Is it an ancient city of Greece? Knowing that someone would ask me these questions, I consulted the *Columbia Encyclopedia* and learned that Cappadocia was the ancient Hittite state located in what is now central Turkey. Recently, I was asked to be on the thesis committee of a young doctoral candidate in our Institute for Medical Humanities. His dissertation proposal referred to philosophies (e.g., hermeneutics and phenomenology) that I had never heard of. These topics were described in the *Columbia Encyclopedia* in a brief capsule format that did not overwhelm my untrained and uneducated mind. Therefore, I have become a fan of small-volume encyclopedias. They are quite useful.

Why, then, has a publisher not produced such encyclopedias for the fields of medicine and the biological sciences? In fact, indeed one has. Elsevier has published several such encyclopedias, including *The Encyclopedia of Cancer* (now in its second edition), *The Encyclopedia of Hormones*, and *The Encyclopedia of Toxicology*. Now, under the leadership of Editor-in-Chief Leonard R. Johnson, Ph.D., a respected gastrointestinal scientist, educator, editor, and author, Elsevier has published *The Encyclopedia of Gastroenterology*. Dr. Johnson has assembled a cadre of 15 Associate Editors, each a highly respected expert in one or more of the topics featured in the book. They have brought together over 700 authors to write 477 articles, divided into three volumes.

These articles go a long way toward covering the entire gamut of gastroenterology and hepatology and do so in an expert fashion. They cover gastrointestinal and hepatic diseases, as well as syndromes, diagnostic and treatment modalities, and physiological and pathological processes. Where necessary, discussions of some of the diseases are divided into separate articles describing the condition in pediatric patients and adult patients. The articles are easy to read, yet comprehensive, and usually encompass both the basic science and the clinical aspects of that disease or process. Each article begins with a glossary of terms that allows the uninitiated to read the article by filling in gaps in understanding; a brief abstract that gives a concise, but comprehensive, overview of the subject matter follows the glossary.

Modern gastroenterology and gastrointestinal science lend themselves well to an encyclopedia format. Gastroenterology is a broad clinical field comprising issues that concern human behavior and psychology, other disciplines that are useful for understanding functional gastrointestinal diseases, such as dyspepsia and irritable bowel syndrome, and very technical sciences that encompass endoscopy as a diagnostic and therapeutic tool and often surgery as definitive treatment. In the middle of the spectrum is classical internal medicine as it relates to the gastrointestinal tract and liver. Furthermore, the behavioral, medical, endoscopic, and surgical approaches may differ considerably for pediatric patients versus adult patients.

As regards basic gastrointestinal science, the gastrointestinal tract does more than simply process and assimilate nutrients and water through the action of its digestive enzymes and secretory and absorptive processes. Gastrointestinal science also encompasses diverse fields such as endocrinology, immunology, and the neurosciences. If all the endocrine cells of the gastrointestinal tract were combined into one organ, it would be the largest endocrine organ in the human body. Similarly, the mucosal immune cells and the gastrointestinal-associated lymphatic tissue together constitute perhaps the largest organ of the immune system in the body. Furthermore, this entire, complex epithelial, secretory, absorptive, endocrine,

and immunological organ is controlled by its own intrinsic brain and nervous system, the enteric nervous system.

Gastroenterology is made even more complicated by the frequency with which diseases of this system occur and by its close relationship to other disciplines. Gastrointestinal cancer is the second most common type of cancer, if men and women are considered together. The broad field of nutrition borders closely on and is intertwined with gastroenterology. Finally, the intestinal tract is colonized by commensal microbiota that are crucial for optimal health. Little is known about these microorganisms, but it is beginning to be understood that they may be a vehicle for the treatment or prevention of disease through probiotics.

This broad view of gastroenterology and gastrointestinal science must have made it difficult for the Editors to choose the individual articles that make up these three volumes. However, I find the list to be fairly complete and each article to be a good mixture of basic knowledge and clinical information. If certain subject areas are not represented as specific articles, they are reasonably well covered in other articles that are in the three volumes and can be located in the subject index at the end of the third volume.

Who will use *The Encyclopedia of Gastroenterology* and why? I believe that the range of potential users is wide. For example, medical students often have difficulty with medical textbooks. Either the textbooks are too advanced and the various words and terms are not explained, making it difficult for the student to comprehend the text, or else the content has been reduced to a "mini" textbook version that often lacks substance. I believe that many of the entries in this encyclopedia are geared perfectly for medical students new to clinical medicine. The glossary of terms at the beginning of each article and the abstracts should be extremely helpful for those who are medically naive. Furthermore, the articles are well-crafted combinations of basic science and clinical science and this is useful at the medical student level.

Physicians from other disciplines will undoubtedly find *The Encyclopedia of Gastroenterology* to be a valuable reference work. The explosion of medical knowledge has made it difficult, if not impossible, to keep up with advancements in other areas of medicine. This encyclopedia provides concise descriptions of the various gastrointestinal diseases that are easily readable, complete, and up-to-date. This should be quite useful for the primary care physician or a specialist in another discipline who needs to know about some specific gastrointestinal disease or process.

Basic scientists and nonphysician translational research scientists would certainly benefit from this encyclopedia also. For instance, the mixture of basic science and clinical science information in each article is precisely what the basic scientist needs as he or she writes the Introduction or Discussion sections of publications or the Background section of grant applications. In addition, the encyclopedia would prove quite valuable in rapidly bringing scientists up to date in a specific area of gastrointestinal disease. In this era of transgenic animals, it is not uncommon for the scientist who has been conducting research in a specific field, for example, immunology or rheumatology, to create a new knockout mouse that presents with a gastrointestinal phenotype rather than a rheumatological phenotype. Thus, the scientist who has spent his or her career gaining an understanding of rheumatologic disease will need to quickly acquire a basic understanding of Crohn's disease and ulcerative colitis.

Finally, the gastroenterologist or gastrointestinal scientist can certainly utilize this encyclopedia as well. It is impossible to stay abreast of all areas of gastroenterology and gastrointestinal science and yet the overlapping disciplines within gastroenterology may demand a more detailed knowledge of an otherwise distant field of expertise. Thus, I look forward to having these three volumes on my bookshelf. They will be helpful in my clinical practice of gastroenterology and also helpful to me as a scientist and to other research scientists in my laboratory.

In summary, the Editors should be proud of their contribution to the knowledge base of gastroenterology. They have found a niche in our field that has hitherto not been occupied. There will continue to be a need for more elementary dictionaries and for highly detailed, advanced textbooks and monographs. *The Encyclopedia of Gastroenterology* will play a role in the middle of this spectrum and should be extremely valuable to a wide range of users. I believe that the three volumes will find their way onto the bookshelves of most medical libraries, as well as those of individual practitioners of medicine and active gastrointestinal investigators. *The Encyclopedia of Gastroenterology* is an extremely useful addition to our field.

DON W. POWELL

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*Professor, Cellular Physiology and Molecular Biophysics*
*Associate Dean for Research*
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# PREFACE

The *Encyclopedia of Gastroenterology* bridges basic science and clinical gastroenterology in a way that should appeal to the expert researching a topic outside his or her field of expertise as well as to students and the educated public. Although some articles on the basic medical sciences stand alone, most integrate these topics with areas of clinical medicine. These volumes appear at a time when general interest in, and knowledge of, the gastrointestinal tract is expanding at a rapid rate. Research has led to new approaches in the treatment of many gastrointestinal diseases and a plethora of new drugs have been added to the pharmaceutical armamentarium. Diagnostic procedures have advanced remarkably over the past few years, leading to an increased understanding of how diseases develop and an improved ability to detect them.

The reader will find articles related to all areas of gastroenterology. There are articles covering basic physiology, pharmacology, anatomy, immunology, and microbiology. Others relate these basic fields to specific diseases. Many of these articles are entitled with the name of a disease or pathological condition. When appropriate, nutritional aspects of clinical conditions are emphasized and several articles feature aspects of nutrition. Areas of parasitology of special importance in relation to the gastrointestinal tract are also covered. Separate articles treat topics relating primarily to pediatric gastroenterology and numerous entries are concerned with radiology, endoscopy, and surgery.

The articles are written and organized to serve as convenient, yet comprehensive sources of information. Each of the 477 entries begins with a glossary of cross-referenced terms followed by a brief abstract. Generous use of primary and secondary headings allows the reader to locate material rapidly. Tables and figures emphasize important points and concepts. Each article presents core knowledge, time-tested and generally accepted within the field. As a result, there are no specific references with the entries. Each contribution, however, concludes with a list of references for further reading. Many of these are review articles with comprehensive bibliographies.

This work began with the selection of a number of general areas of coverage. A group of 15 Associate Editors, each of whom is an expert in at least one of these areas, was subsequently recruited. The entire group, along with members of the Elsevier staff, then met for two days in San Diego. That meeting resulted in the refinement of the areas of coverage, selection of individual article topics within those areas, and identification of potential authors. The Associate Editors and I believe that we have covered the important topics of basic and clinical gastroenterology. Each article is written to stand alone as a complete subject, so there is, no doubt, a certain amount of overlap. This, however, should make it easier for the reader to locate a specific piece of information.

A product of this magnitude represents the knowledge and efforts of a large number of individuals. More than 600 authors contributed their expertise to the individual articles. I am especially grateful to those who produced articles on short notice, so that our deadline could be met. An outstanding group of 15 Associate Editors was the foundation for this project. Due to their great breadth of knowledge, they were able to propose topics for articles and recommend the authors to write them. They then recruited the authors and edited the completed articles.

Finally, I acknowledge the contributions of the staff at Elsevier. The *Encyclopedia of Gastroenterology* was initiated and supported by Jasna Markovac, Sr. Vice President, Elsevier, Science and Technology. Nick Panissidi, Senior Developmental Editor, was indispensable as he contacted authors and kept up with all article submissions. Pat Gonzalez served as Production Manager, and Tari Paschall, Sr. Publishing Editor, and Judy Meyer, Associate Publishing Editor, provided overall management of the project.

LEONARD R. JOHNSON

# GUIDE TO USING THE ENCYCLOPEDIA

The *Encyclopedia of Gastroenterology* is a comprehensive yet accessible resource describing all significant aspects of the discipline of gastroenterology. This reference work consists of three separate volumes and includes 477 articles written by leading experts in the field. Each entry in the encyclopedia provides a focused description of the given topic, intended to inform a broad spectrum of readers, ranging from academic and clinical gastroenterologists to students and to the interested general public.

In order that you, the reader, will derive the greatest possible benefit from your use of the *Encyclopedia of Gastroenterology*, we have provided this Guide. It explains how the encyclopedia is organized and how the information within it can be located.

## Organization

All of the articles in the *Encyclopedia of Gastroenterology* are arranged in a single alphabetical sequence by title. Articles whose titles begin with the letters A to E are in Volume 1, articles with titles from F to N are in Volume 2, and articles from O to Z are in Volume 3, along with the Subject Index.

So that they can be easily located, article titles generally begin with the key word or phrase indicating the topic, with any generic terms following. Thus, for example, "Colitis, Ulcerative" is the article title rather than "Ulcerative Colitis," and is grouped with the other "Colitis" entries. Similarly, "Nutrient Transport, Regulation of" is the title rather than "Regulation of Nutrient Transport."

## Table of Contents

A complete table of contents for the *Encyclopedia of Gastroenterology* appears at the front of each volume. This alphabetical list of article titles (see page v) is followed by a second contents list (see page xix) in which the titles are listed according to their subject area. The articles have been classified into 25 different subject areas listed below:

Absorption and Secretion
Anatomy and Development
Biliary System
Cancer
Cell Biology
Colitis/Ulcer/Diarrhea
Esophagus
General Symptoms
Hormones and Transmitters
Immunology
Intestines
Liver
Motility
Neurogastroenterology
Nutrition
Overviews
Pancreas
Parasitology
Pediatrics
Pharmacology
Psychology and Behavior
Radiology and Endoscopy
Stomach
Surgery
Systemic Diseases

## Index

A Subject Index is located at the end of Volume 3. This index is the most convenient way to locate a desired topic within the encyclopedia and thus it should be the starting point for any reader seeking to find a topic. The entries in the index are listed alphabetically and indicate the volume and page number where information on this topic can be found.

## Article Format

Articles in the *Encyclopedia of Gastroenterology* are arranged in a standard format, as follows:

Title and Author
Glossary
Defining Statement
Body of Article
Cross-References
Further Reading

## Glossary

The Glossary contains terms that are important to an understanding of the article and that may be unfamiliar to the reader. Each term is defined in the context of the particular article in which it is used. The encyclopedia includes approximately 2,000 glossary terms. For example, the article "Glycogen Storage Disease" includes the following glossary entries (among others):

**gluconeogenesis** Formation of new glucose from noncarbohydrate substrates, including various amino acids, lactate, pyruvate, and glycerol.

**glycogenolysis** Intracellular breakdown of glycogen to glucose.

## Defining Statement

The text of each article begins with an introductory paragraph that is displayed in boldface and set off from the rest of the article. This introduction defines the topic under discussion and summarizes the content of the article. For example, the entry "Celiac Disease" begins with the following defining paragraph:

**Celiac disease, a chronic inflammatory condition associated with small intestinal injury induced by gluten exposure, results in malabsorption of different nutrients. It is associated with multiple other medical conditions. The diagnosis relies on characteristic findings of small intestinal biopsy. Patients with celiac disease usually respond quickly to a gluten-free diet. The disease requires a lifelong commitment to a gluten-free diet to prevent recurrence of symptoms and other potential consequences.**

## Cross-References

All of the articles in the Encyclopedia have cross-references to other articles. These appear at the conclusion of the article text, preceding the Further Reading section. The Encyclopedia contains over 2,700 cross-references in all. The cross-references indicate related articles that can be consulted for further information on the same topic, or for information on a related topic. For example, the article "Diarrhea" provides the following cross-references:

**Antibiotic-Associated Diarrhea • Anti-Diarrheal Drugs • Bacterial Toxins • Carbohydrate and Lactose Malabsorption • Diarrhea, Infectious • Diarrhea, Pediatric • Gastroenteritis • Malabsorption • Malnutrition • Pancreatic Function Tests •** Traveler's Diarrhea

## Further Reading

The Further Reading section appears as the last element in an article. It lists recent secondary sources to aid the reader in locating more detailed or technical information. Review articles and research papers that are important to an understanding of the topic are also listed. For example, the article "Gastroesophageal Reflux Disease (GERD)" has the following references (among others):

Achem, S. R., Kolts, B. E., MacMath, T., Richter, J., Mohr, D., Burton, I., and Castell, D. O. (1997). Effects of omeprazole versus placebo in treatment of noncardiac chest pain and gastroesophageal reflux. *Digest. Dis. Sci.* 42, 2138–2145.

DeVault, K. R., and Castell, D. O. (1999). Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. *Am. J. Gastroenterol.* 94, 1434–1442.

Hunter, J. G., Trus, T. L., Branum, G. D., Waring, J. P., and Wood, W. C. (1996). A physiologic approach to laparoscopic fundoplication for gastroesophageal reflux disease. *Ann. Surg.* 223, 673–685.

Ours, T. M., Kavuru, M. S., Schilz, R. J., and Richter, J. E. (1999). A prospective evaluation of esophageal testing and a double-blind, randomized study of omeprazole in a diagnostic and therapeutic algorithm for chronic cough. *Am. J. Gastroenterol.* 94, 3131–3138.

Spechler, S. J., Lee, E., Ahnen, D., *et al.* (2001). Long-term outcome of medical and surgical therapies for gastroesophageal reflux disease: Follow-up of a randomized controlled trial. *J. Am. Med. Assoc.* 285, 2331–2338.

Waring, J. P. (2001). Surgical and endoscopic treatment of gastroesophageal reflux disease. *Gastrointest. Clin. North Am.* 31, S89–S109.

The Further Reading references are for the benefit of the reader; they provide the author's recommendations for more information on the given topic. Thus they consist of a limited number of entries. They do not represent a complete listing of all the sources consulted by the author in preparing the paper.

O

# Obesity, Treatment of

GEORGE A. BRAY
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**body mass index** A measure of normal weight and overweight [weight (in kilograms)]/[height (in centimeters)]$^2$.
**gastric bypass** Construction of a small (10–30 ml) proximal gastric pouch by stapling across the stomach or complete resection from the rest of the stomach, connected to a segment of jejunum brought up at a Roux-en-Y limb.
**obesity** Body mass index is $>30\,kg/m^2$.
**overweight** Body mass index in the range of $25–29.9\,kg/m^2$.

**Obesity produces complications that involve nearly all major organ systems. The major gastrointestinal medical complications associated with obesity include gallstones, nonalcoholic fatty liver disease, and possibly gastroesophageal reflux disease.**

## INTRODUCTION

As the epidemic of obesity has grown over the past 20 years, the need to understand its causes and apply this knowledge to the treatment of obesity has become ever more urgent. As medical science's understanding of obesity increases, novel ideas about techniques, strategies, molecules, and procedures that can be used to curtail the devastating effects of this epidemic will emerge. This article will focus on five different approaches to the treatment of obesity. These are behavioral therapy, diet, exercise, medications, and surgery. As there is only space for a brief discussion of each, the reader is referred to other sources for more details (see Further Reading). Since obesity is an imbalance between the energy that is ingested and the energy that is expended, any treatment must have an effect on one or both sides of the energy balance equation. This concept is easily applied to diet, which aims to reduce food intake, and exercise, which aims to raise energy expenditure. The subtleties of this concept, when applied to medications, are more complex.

## BEHAVIOR THERAPY

Over the past 30 years, there has been a steady improvement in behavioral techniques that were originally introduced only in 1967 by Stuart in a classic paper. The basic elements of any behavioral program focus on three things: identifying the antecedents to eating and changing them; characterizing an individual's eating style and improving it; and providing rewards for improved eating behavior. With programs that last up to 24 weeks, the retention is usually more than 75% and weight losses can be up to 10% of initial body weight.

Retrospective analysis has shown that several strategies are particularly useful. These include self-monitoring of one's eating habits, eating a lower fat diet, being more physically active, and developing a support system to help reward successful behavior. Providing structured meal plans has proven to be an additional useful strategy. These can be meal plans, written menus, or portion-controlled foods. The use of the internet has also proven to be a potentially valuable approach to delivering behavioral therapy. The major problem with behavioral strategies is that patients tend to regain weight after leaving the program. Recent focus has concentrated on ways of continuing the impact of the program over longer periods of time.

Overweight adolescents are a good target for preventive strategies using behavior therapy, because good 10-year data show that intervention for this group can reduce the degree of overweight into adult life. Data on the efficacy of behavior programs carried out in controlled settings show that weight losses average nearly 10% in trials lasting more than 16 weeks. The problem with behavioral therapy is that regaining weight once the behavior treatment ends is frequent. At least one long-term study showed that behavioral therapy could provide long-term weight loss, providing it was continued.

## DIET

### Calories

The essential element of any diet is that it reduces the total caloric intake. Many different diets have been recommended over the past 150 years since Mr. Banting published his famous pamphlet in 1863. One of the most

 

popular themes has been the low-carbohydrate diet. The fact that new diets continue to appear suggests that none of them have a magic formula because if one did, none of the others would have succeeded in the marketplace.

### Fat

There are a number of elements of an effective diet that anyone can incorporate with potential benefit. The observation from behavioral therapy that a low-fat diet is what successful patients adopt suggests that this would be a useful strategy. Several reviews have shown that low-fat diets are associated with weight loss. The initial weight is one variable predicting the magnitude of the response (overweight people lose more than do normal weight people). A second variable is the amount of fat removed from the diet—the greater the reduction, the more weight is lost. Palatability of the diet may be another factor. A recent study showed that replacing fat with olestra, a nondigestible fat substitute, reduced body weight by 6% and body fat by nearly 20% over 9 months, whereas a standard reduced-fat diet with the same available fat was relatively ineffective. However, a very-low-fat diet can be difficult for many people to adhere to. For this reason, the best advice is to reduce saturated and *trans*-fatty acids and to lower total fat to as near 25% as possible for the individual.

### Carbohydrate and Fiber

Carbohydrate and both digestible and indigestible fiber intake can affect food intake. Although recent studies show that substituting starch for sugar does not produce greater weight loss, the type of digestibility of that carbohydrate may play a role. The glycemic load, which is the glycemic index times the carbohydrate intake, may be important. In the Nurses Health Study, the glycemic load was related to the risk of developing heart disease and diabetes. Diets with a low glycemic index, i.e., with a lower rise in glucose, produce more satiety than do diets with a high glycemic index.

### Breast Feeding

Several recent studies suggest that the length of breastfeeding affects childhood obesity. In a large German study of more than 11,000 children, von Kries *et al.* showed that the duration of breastfeeding as the sole source of nutrition was inversely related to the incidence of obesity, defined as a weight above the 95th percentile, when children entered the first grade. In this study, the incidence was 4.8% in children with no breastfeeding, falling in a graded fashion to 0.8% in children who were fed solely from the breast for 12 months or more. A second large report also showed that breastfeeding reduced the incidence of overweight adolescents. The third report with fewer subjects and more ethnic heterogeneity failed to show this effect. However, the possibility that lengthening the duration of breastfeeding could reduce the future risk of obesity is another reason to recommend breastfeeding for at least 6 to 12 months.

### Dietary Calcium

Nearly 20 years ago, McCarron *et al.* reported that there was a negative relationship between body mass index and dietary calcium intake in the data collected by the National Center for Health Statistics. More recently, in 1999, Zemel *et al.* found that there was a strong inverse relationship between calcium intake and the risk of being in the highest quartile of body mass index. These studies have prompted a reevaluation of clinical trials that have given calcium supplements orally. In the prospective trials, subjects receiving calcium had a greater weight loss than did subjects receiving placebos. Increasing calcium from 0 to nearly 2000 g/day was associated with a reduction in body mass index (BMI) of approximately 5 BMI units. These data might suggest that low calcium intake plays a role in the current epidemic of obesity.

## EXERCISE

Exercise is an obvious way to increase energy expenditure. This is desirable for all Americans and would be beneficial for reducing cardiovascular risks. However, for many people who are overweight, exercise can be a challenge, because they are already expending more energy doing everyday activities. Thus, for many such patients, a simple walking program can be the best approach. That this is valuable is shown by the Diabetes Prevention Program, where a lifestyle program of diet and exercise produced a 58% reduction in the conversion of patients with impaired glucose tolerance to diabetes mellitus.

With substantial amounts of supervised exercise, significant weight loss can be obtained. However, for many people, exercise adds little extra weight loss to a dietary program aimed at weight loss, probably because people do not maintain the amount of exercise that is prescribed. Some reports suggest that exercise may conserve body protein during dieting, but others do not.

The most beneficial part of an exercise program comes when trying to maintain a lower body weight. In a survey of people who were successful at maintaining

weight, exercise was maintained at a level significantly above that in people without a weight problem.

## MEDICATIONS

Medication should be seriously considered for clinically overweight individuals, defined as individuals with a body mass index above 30 kg/m$^2$, or those with diabetes, impaired glucose tolerance, hypertension, or heart disease combined with a BMI above 27 kg/m$^2$. Two strategies can be used to treat individuals who are clinically overweight. If they have co-morbidities, individual drugs can be used to treat each co-morbidity; i.e., patients can be treated for their diabetes, hypertension, dyslipidemia, and sleep apnea. Alternatively, or in addition, patients with a BMI $> 30$ kg/m$^2$ could be treated with anti-obesity drugs. Current drugs include appetite suppressants that act on the central nervous system and orlistat, which blocks pancreatic lipase. The availability of these agents differs from country to country and any physician planning to use them should be familiar with the local regulations. Most of the drugs on the market were reviewed and approved more than 20 years ago and are approved for short-term use only. The basis for the short-term use is twofold. First, almost all the studies of these agents are short-term. Second, the regulatory agencies are concerned about the potential for abuse and thus have restricted their prescription to "only a few weeks," which is usually interpreted as up to 12 weeks. The withdrawal of fenfluramine and dexfenfluramine from the market in 1997 following the development of valvular heart disease in patients treated with these drugs further compounds the concern of health authorities about the safety of appetite suppressants. Because of the regulatory limitations and the lack of longer-term data on safety and efficacy, the use of the drugs approved for short-term treatment must be carefully justified. These drugs may be useful in initiating treatment and in helping a patient who is relapsing, but only for a few weeks.

Sibutramine (Meridia; Reductil) is approved in many countries for long-term use. The evidence shows that weight loss of 10% or more can be produced with this drug. The side effect profile includes dry mouth, asthenia, insomnia, and constipation. It also produces a small increase in heart rate of 2–5 beats per minute and a small rise in blood pressure of 2–4 mm Hg. Clinical data show no evidence of valvulopathy. Blood pressure should be followed carefully and the drug may be inappropriate in patients with stroke, congestive heart failure, or recent myocardial infarction. It should not be used with other serotonergic drugs or drugs that inhibit monoamine oxidase.

Orlistat (Xenical), a drug that blocks intestinal lipase, has been approved for long-term use in many countries. In clinical trials lasting up to 4 years, orlistat was associated with a mean weight loss of up to 10% at the end of 1 year in patients who were prescribed a 30% fat diet. As might be expected, because the drug blocks pancreatic lipase in the intestine, fecal fat loss is increased. Major side effects related to the release of undigested triglyceride occurred in some patients, usually within the first month, and were reported with reduced frequency over time, indicating that patients learned to use the drug effectively in relation to dietary intake of fat. The effective use of this medication requires that physicians and their staff members provide good dietary counseling to patients.

The combination of ephedrine and caffeine is a third compound for which a randomized clinical trial has been published by Astrup *et al.* Over 6 months, the patients treated with ephedrine and caffeine lost more weight than did the placebo-treated group or the two groups treated individually with ephedrine or caffeine. This research has been used for marketing of herbal preparations that contain ephedra alkaloids with or without caffeine. Two clinical trials by Boozer *et al.* have shown significantly greater weight loss with an herbal ephedra/caffeine preparation than with placebo.

The epidemic of obesity, the discovery of genes that produce obesity, and a slim armamentarium for treatment of obesity have spurred many pharmaceutical companies to search for new agents. These agents can be divided into two categories: compounds that are in clinical trials with suggestive data and new molecules just entering the clinical arena. In the former category are bupropion, leptin, and topiramate. Bupropion is approved by the Food and Drug Administration (FDA) as an antidepressant. Two recent studies show that it produces weight loss. Leptin is the peptide produced primarily in adipose tissue. When deficient, it produces massive obesity. Leptin-deficient patients respond to leptin with weight loss, suggesting that leptin might be clinically useful if the proper way of delivering it can be found. The third molecule, topiramate, is an anticonvulsant approved by the FDA for this purpose. Several studies now suggest that topiramate produces weight loss in patients receiving it for their epilepsy. Clinical trials with this compound are currently under way.

A number of other molecular targets could serve as the basis for clinically useful drugs. These molecules can be divided into those that have a peripheral mechanism of action and those that act on the brain. Thermogenic β-adrenergic receptors are one target that have been investigated for more than 15 years, but as yet

no clinically useful molecule has been identified. Cholecystokinin reduces food intake in animals and humans. To date, no useful molecules that work through this receptor have been identified. Glucagon-like peptide 1 (GLP-1) is processed from the enteroglucagon molecule by gastrointestinal (GI) cells. Infusion of GLP-1 into lean and obese human beings reduces food intake and molecule agonists to this receptor system are under development. Ghrelin, produced primarily in the stomach, has been recently identified and shown to increase food intake when given peripherally or centrally. Antagonists to this receptor system offer potential for future molecules with which to treat obesity. Finally, the pentapeptide enterostatin, cleaved from pro-colipase in the intestinal lumen, reduces food intake and primarily fat intake. This molecule or similar molecules might have interesting potential for modulation of clinical fat intake.

Neuropeptide Y is one of the most potent stimulators of food intake when it is injected into the brain. Several abstracts suggest that this may be a useful target, with molecules aimed at either the Y-1 or the Y-2 receptor. Loss of the melanocortin-4 receptor produces massive obesity in mice, suggesting that molecules aimed at this receptor could be useful. The endogenous signal for this system is probably α-melanocyte-stimulating hormone (α-MSH), which is produced from proopiomelanocortin. Another endogenous molecule, agouti-related peptide (AGRP), inhibits the effect of α-MSH. Modulation of the receptors for AGRP or α-MSH would be two potential targets. The peptides mentioned above are under the control of circulating leptin acting on receptors in the arcuate nucleus of the hypothalamus. Cocaine–amphetamine-regulated transcript (CART) is a fourth molecule in the brain that modulates, and reduces, food intake. A receptor agonist that mimicked CART might also be an attractive target. At least two other hypothalamic peptides need to be considered in this discussion. The first is melanocortin-concentrating hormone. Animals overexpressing this peptide are heavier than controls and disabling the production of this peptide produces leanness. Other hypothalamic peptides are corticotropin-releasing hormone (CRH) and urocortin, two variants that differentially bind to CRH R1 and CRH R2. CRH reduces food intake and modulating its activity would be another potential mechanism to reduce food intake.

## SURGERY

Surgical intervention was initiated more than 40 years ago with operations that shortened the absorptive surface available to GI contents by various bypass operations. At present, the principal operations are the gastric bypass, the vertical banded gastroplasty, and the gastric band, which allows a constrictive band around the stomach to be expanded by injecting saline into a subcutaneous reservoir. With the introduction of laparoscopic surgery and advancement in the skill of surgeons using this surgery during the 1990s, the safety of these procedures improved. Although originally recommended for people with a body mass index above 40 kg/m$^2$, the studies showed marked benefits to patients having this surgery, which suggests that the BMI should be reduced to 35 kg/m$^2$ or even lower if there are significant risks associated with the obesity.

## BENEFITS OF INTENTIONAL WEIGHT LOSS

Because the weight loss after gastric surgery is more sustained than after other methods of weight reduction, much of the data on the benefits of weight loss are derived from those patients. Although the data are not entirely clear, studies indicate that intentional weight loss $\geq$20 pounds has been associated with an approximately 25% reduction in obese and overweight patients who have an obesity-related illness, especially type 2 diabetes mellitus. Other benefits of modest sustained weight loss include improved cardiovascular function, better control of type 2 diabetes mellitus, dyslipidemia, and hypertension. Improved respiratory function with less obstructive sleep apnea and improved reproductive and urinary tract function in women require considerably more weight loss.

Although the relationship between obesity and factors that dispose to gastroesophageal reflux disease is not clear, significant weight loss after gastric surgery caused resolution of symptoms, even before significant weight loss occurred. Gallstones may increase in incidence in obesity and rapid weight loss increases bile cholesterol supersaturation, increasing the risk of new gallstones. Nonalcoholic fatty liver disease (NAFLD) is associated with the metabolic syndrome (increased insulin, hypertension, and hyperlipidemia), perhaps as an earlier stage before obesity or diabetes mellitus develops. A gradual weight loss may improve hepatic chemistries and liver size, but rapid weight loss (e.g., after gastric surgery) may exacerbate NAFLD.

### See Also the Following Articles

**Appetite • Diabetes Mellitus • Dietary Reference Intakes (DRI): Concepts and Implementation • Gastric Surgery • Minimally Invasive Surgery • Prader–Willi Syndrome • Satiety**

## Further Reading


Bray, G. A., Blackburn, G. L., Ferguson, J. M., Greenway, F. L., Jain, A. K., Mendel, C. M., Mendels, J., Ryan, D. H., Schwartz, S. L., Scheinbaum, M. L., and Seaton, T. B. (1999). Sibutramine produces dose-related weight loss. *Obesity Res.* 7, 189–198.

Bray, G. A., and Greenway, F. L. (1999). Current and potential drugs for treatment of obesity. *Endocr. Rev.* 20, 805–875.

Bray, G. A., and Popkin, B. M. (1998). Dietary fat intake does affect obesity! *Am. J. Clin. Nutr.* 68, 1157–1173.

Bray, G. A., and Tartaglia, L. A. (2000). Medicinal strategies in the treatment of obesity. *Nature* 404, 672–677.

Davies, K. M., Heaney, R. P., Recker, R. R., Lappe, J. M., Barger-Lux, M. J., Rafferty, K., and Hinders, S. (2000). Calcium intake and body weight. *J. Clin. Endocrinol. Metab.* 85, 4635–4638.

Freedman, M. R., King, J., and Kennedy, E. (2001). Popular diets: A scientific review. *Obesity Res.* 9, 1S–40S.

Klein, S., Wadden, T., and Sugerman, H. J. (2002). AGA technical review on obesity. *Gastroenterology* 123, 882–932.

Ravussin, E., and Bouchard, C. (2000). Human genomics and obesity: Finding appropriate drug targets. *Eur. J. Pharmacol.* 410, 131–145.

Roberts, S. B. (2000). High-glycemic index foods, hunger, and obesity: Is there a connection? *Nutr. Rev.* 58, 163–169.

Sjostrom, C. D., Lissner, L., Wedel, H., and Sjostrom, L. (1999). Reduction in incidence of diabetes, hypertension and lipid disturbances after intentional weight loss induced by bariatric surgery: The SOS Intervention Study. *Obesity Res.* 7, 477–484.

Sjostrom, L., Rissanen, A., Andersen, T., Boldrin, M., Golay, A., Koppeschaar, H. P., and Krempf, M. (1998). Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. European Multicentre Orlistat Study Group. *Lancet* 352, 167–172.

Tuomilehto, J., Lindstrom, J., Eriksson, J. G., Valle, T. T., Hamalainen, H., Ilanne-Parikka, P., Keinanen-Kiukaanniemi, S., Laakso, M., Louheranta, A., Rastas, M., Salminen, V., and Uusitupa, M. (2001). Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N. Engl. J. Med.* 344, 1343–1350.

von Kries, R., Koletzko, B., Sauerwald, T., von Mutius, E., Barnert, D., Grunert, V., and von Voss, H. (1999). Breast feeding and obesity: Cross sectional study. *Br. Med. J.* 319, 147–150.

Wing, R. (2002). Behavioral approaches to the treatment of obesity. *In* "Handbook of Obesity" (G. A. Bray and C. Bouchard, eds.), 2nd Ed. Dekker, New York, in press.


# Occult Gastrointestinal Bleeding


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**capsule wireless endoscopy** Use of a small camera containing a capsule that is ingested to evaluate the gastrointestinal tract. Typically used to investigate bleeding sources in the small intestine.

**hematemesis** Vomiting of blood; indicates an upper gastrointestinal site of bleeding.

**hematochezia** Bright red blood per rectum; may or may not be mixed with stool.

**Meckel's diverticulum** A 2- to 6-cm outpocketing of the ileum along the antimesenteric border, usually located 50 to 180 cm proximal to the ileocecal valve.

**melena** Tarry, foul-smelling black stools.

**Gastrointestinal bleeding is one of the most common problems in medicine. Bleeding from the upper and lower gastrointestinal tracts is recognized as a major source of disease-related morbidity and, on occasion, mortality. Occult gastrointestinal bleeding is even more common than upper and lower gastrointestinal bleeding. Patients may present with bleeding that is truly hidden (occult); this form of bleeding is extremely common and can even be considered to be pervasive. Patients may instead have clinically obvious bleeding, but the blood is from a source in the gastrointestinal tract that is difficult to identify; this type of occult bleeding has been termed "obscure gastrointestinal bleeding." The clinical spectrum of occult gastrointestinal bleeding is therefore expansive and may encompass any of a number of clinical scenarios. Because patients may present with massive obvious bleeding or may be entirely unaware that they are bleeding, gastrointestinal bleeding afflicts inpatients as well as outpatients.**

## INTRODUCTION

Protocols for evaluation and management of patients with gastrointestinal bleeding have undergone many recent advances. Nonetheless, the fundamental clinical

lip lesions may be seen with Peutz–Jeghers syndrome, cutaneous tumors suggest neurofibromatosis, and purpura are consistent with vascular disease (Henloch-Schönlein syndrome or polyarteritis nodosa). Abdominal pain (peptic ulcer, pancreatitis, ischemia), abdominal masses, lymphadenopathy (malignancy), and splenomegaly (cirrhosis, splenic vein thrombosis) are important to detect.

### Initial Patient Assessment

The first step in all forms of gastrointestinal bleeding is to assess the urgency of bleeding. Therefore, hemodynamics are the initial focal point and remain the gold standard for assessment of the overall clinical well being of the patient. Features of the history and physical examination provide critical clues not only about the cause of bleeding, but also about the severity of bleeding. "Bedside" tools are critical in initial assessment of the patient. Vital signs are essential in helping to gauge the severity of bleeding. Additionally, features of the history and physical exam provide critical information. For example, patients with brown stool are unlikely to have aggressive bleeding. Patients passing numerous stools containing melena—even in the absence of a positive nasogastric lavage—are likely to have aggressive ongoing bleeding. Patients with infrequent stools are unlikely to be actively bleeding. Patients with a history of coffee-ground emesis or even hematemesis, normal appearing stools, and normal vital signs have had a trivial bleed.

### Laboratory Evaluation

The laboratory evaluation most often focuses on the hematocrit. However, it is important to recognize that the hematocrit, particularly when determined soon after the onset of bleeding, may not accurately reflect blood loss. Equilibration with extravascular fluid and subsequent hemodilution require several hours. In contrast, patients who bleed small amounts of blood over long periods of time develop iron deficiency, and despite the presence of a low hematocrit may be entirely hemodynamically stable. The mean corpuscular volume (MCV) is often an important clue in these patients; additionally, the ferritin level is used to establish a diagnosis of iron deficiency. It is important to emphasize that ferritin levels of even 50 μg/ml are consistent with iron deficiency anemia.

The blood urea nitrogen (BUN) may be mildly elevated in patients with upper GI bleeding. The elevation is typically out of proportion to elevation in serum creatinine, due to breakdown of blood proteins to urea by intestinal bacteria as well as from a mild reduction in glomerular filtration rate.

### Clinical Localization of Bleeding

It is useful to determine the source of bleeding so as to direct investigation; this can often be accomplished with a careful history and physical examination. Hematemesis indicates an upper gastrointestinal source of bleeding. Melena indicates that blood has been in the gastrointestinal tract for extended periods of time. Melena is usually the result of upper gastrointestinal bleeding, but can be a result of distal small bowel and even right-sided colonic bleeding. The latter occurrence, which is relatively uncommon, requires the volume of bleeding to be too small to cause hematochezia but sufficient to supply enough hemoglobin for degradation. Hematochezia typically is a result of colonic bleeding, although an upper gastrointestinal lesion may bleed briskly enough to cause hematochezia. Somewhere around 10% of all patients with rapid bleeding from an upper source will pass bright red blood per rectum. Other clues to an upper gastrointestinal source of bleeding include hyperactive bowel sounds and an elevation in BUN out of proportion to creatinine. The use of nasogastric lavage can further help localize bleeding.

## OCCULT BLEEDING

### Obscure Bleeding

A standard diagnostic evaluation with upper and lower endoscopy, tagged red blood cell (RBC) scintigraphy, and visceral angiography is able to identify the source of bleeding in the majority of patients. However, in approximately 5% of patients, the source will remain obscure after a diagnostic evaluation. Even more problematically, some of these patients experience recurrent gastrointestinal bleeding that can not be easily ascribed to a definite site. These patients represent a considerable management challenge.

#### *Differential Diagnosis*

The differential diagnosis in patients with obscure gastrointestinal bleeding encompasses all of the lesions that can bleed in the upper and lower gastrointestinal tracts. The most common causes of obscure gastrointestinal bleeding are highlighted in Table II. The most common lesion is vascular ectasia. These lesions are often found in the small intestine, but can be identified in any location.

TABLE II Causes of Obscure Gastrointestinal Bleeding[a]

| |
|---|
| Vascular ectasias[b] |
| Small bowel neoplastic lesions |
| Hemosuccus pancreaticus |
| Hemobilia |
| Aortoenteric fistula |
| Dieulafoy's ulcer (stomach more frequently than other sites) |
| Meckel's diverticulum |
| Extraesophageal varices (gastric, small bowel, colonic) |
| Diverticula (especially small intestinal) |

[a] From Rockey, D.C. (2002). Used with permission from W. B. Saunders.

[b] Small intestinal lesions are particularly important.

### *Evaluation*

The approach to evaluation should proceed along a standard algorithm (Fig. 1). Initially, easily "overlooked" lesions should be considered. Such lesions include Dieulafoy's lesions, gastric and duodenal varices, diverticula, aortoenteric fistula, hemobilia, hemosuccus pancreaticus, and, in young patients, Meckel's diverticulum. Thus, repeat endoscopy directed at the most likely site of bleeding is usually warranted. Reexamination of the upper gastrointestinal tract within reach of a standard gastroscope will identify lesions in a substantial proportion of patients. Importantly, however, familiarity with rare and/or subtle bleeding lesions is required. If a lesion cannot be identified, further evaluation depends on the briskness of bleeding. In those with active bleeding, technetium-99 radionuclide scanning or angiography should be performed. Technetium scanning, although sensitive (reportedly, as little as 0.1 ml/minute can be detected), is useful only to confirm the site of bleeding, and available literature assessing its impact on management has been disappointing. Mesenteric angiography is less sensitive (requiring a bleeding rate $>0.5$ ml/minute) than technetium scanning but reportedly more often identifies the site of bleeding, perhaps due to selection bias in published studies. In selected situations, other diagnostic tests (computed tomography, Meckel's scan) may be helpful. In those with subacute bleeding in whom repeat endoscopies are negative, the focus of investigation should be broadened to include the small intestine. The lesions most commonly identified as bleeding sites in the small bowel

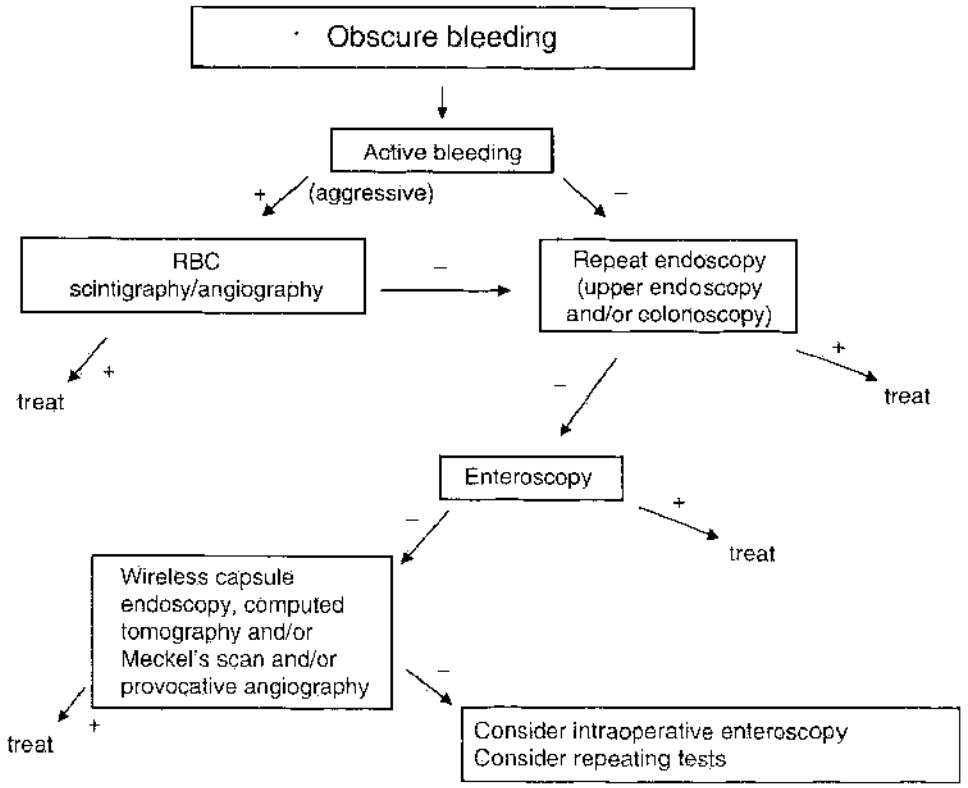


FIGURE 1 Scheme for evaluation of obscure gastrointestinal bleeding. RBC, Red blood cell. Adapted with permission from Rockey, D. C. (2002). Gastrointestinal bleeding. *In* "Sleisenger & Fordtran's Gastrointestinal and Liver Disease" (M. Feldman *et al.*, eds.). 7th Ed. W. B. Saunders, Philadelphia.

include tumors and vascular ectasias, which vary in frequency depending on age. In patients less than 25 years of age, Meckel's diverticula are the most common source of small bowel bleeding; in those between 30 and 50 years old, tumors are the most common abnormalities, and vascular ectasias predominate in the elderly.

Once the upper and lower gastrointestinal tracts have been excluded as a source of bleeding, the focus of evaluation should shift to the small bowel. This can be accomplished with standard small bowel follow-through, enteroclysis, push enteroscopy, sonde enteroscopy, intraoperative enteroscopy, or, most recently, wireless capsule endoscopy. We prefer endoscopic evaluation over radiologic evaluation because of the ability to identify flat lesions such as vascular ectasia, which may be missed by barium studies. Push enteroscopy should probably be the first test; several recent reports suggest that push enteroscopy is able to identify a substantial number of gastrointestinal lesions in patients with obscure gastrointestinal bleeding. Sonde enteroscopy is limited by the inability to biopsy lesions or make therapeutic interventions. Wireless capsule endoscopy is rapidly gaining favor. Initial results with this test are encouraging and demonstrate that it is capable of identifying lesions that could be considered a source of bleeding in up to 30–40% of patients.

An alternative approach to the diagnosis of recurrent, obscure bleeding is to reactivate or augment bleeding with the use of vasodilators, anticoagulants, and/or thrombolytics in association with tagged RBC scintigraphy or visceral angiography. This approach is attractive in principle, but may be dangerous in practice and needs to be studied further.

### *Treatment and Outcome*

Specific treatment for the obscure bleeder depends on the abnormality identified. Enteroscopy, which often demonstrates putative bleeding lesions, has not always led to improved outcomes. Enteroscopic cauterization of vascular ectasias has been shown to lead to an improvement in hemoglobin and a reduction in blood transfusion requirements, and can be effective in selected patients. Additionally, only about 50% of patients treated at the time of intraoperative enteroscopy will stop bleeding, indicating that this intervention is not always ideal. Finally, wireless capsule endoscopy is an attractive diagnostic approach in patients with obscure bleeding. However, it and other diagnostic interventions in obscure bleeding have yet to be shown to improve meaningful outcomes. It is important to emphasize that care of these patients requires an experienced and dedicated team.

Small bowel vascular ectasias are the single most common source of bleeding in patients with obscure gastrointestinal bleeding. In general, specific endoscopic and surgical therapy is most successful in those with large focal vascular ectasias. However, because vascular ectasias are often diffuse, endoscopic and surgical interventions are often limited. Hormonal therapy with estrogen/progesterone compounds has been advanced as a medical alternative; whereas some clinicians have reported positive experiences with such pharmacological therapy, controlled trials have failed to show an advantage.

## Fecal Occult Blood

Occult gastrointestinal bleeding is not clinically apparent but rather is manifest by biochemical evidence of blood in the stool or by laboratory evidence of iron deficiency. In these situations, blood loss is often entirely unknown to the patient. When iron deficiency occurs in men or postmenopausal women, it is usually due to occult gastrointestinal blood loss. Occult bleeding can occur from any location in the gastrointestinal tract.

Fecal occult blood is the most common form of occult gastrointestinal bleeding; when fecal occult blood tests have been applied to large populations, up to 16% of those tested are positive. Although fecal occult blood tests were designed to detect colonic bleeding, they detect blood from other lesions in the gastrointestinal tract. The likelihood that these tests will detect blood resulting from gastrointestinal bleeding varies and is dependent on the mechanistic features of the test as well as the anatomic level of bleeding (which influences whether hemoglobin is degraded; Fig. 2). A further critical issue, unrelated to characteristics of fecal occult blood tests per se, is the biology of bleeding gastrointestinal tract lesions, many of which bleed in an irregular fashion. Thus, multiple factors contribute to the ability of fecal occult blood tests to detect bleeding lesions.

### *Types of Fecal Occult Blood Tests*

The prototypical fecal occult blood tests are guaiac based and take advantage of the fact that hemoglobin possesses pseudoperoxidase activity. Guaiac tests are more sensitive for detecting bleeding from the lower than from the upper gastrointestinal tract because hemoglobin is degraded in the gastrointestinal tract (Fig. 2). The likelihood that occult blood will be detected by a positive guaiac test is generally proportional to the quantity of fecal heme, which in turn is related to the size and location of the bleeding lesion.

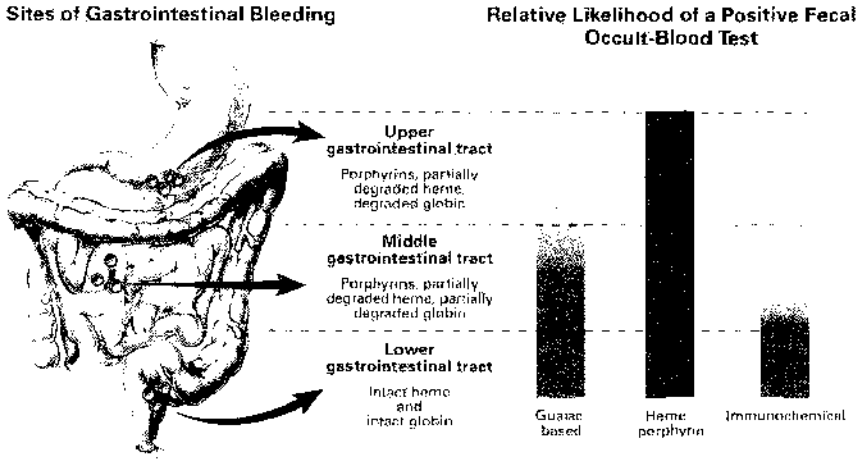


FIGURE 2 Intraluminal hemoglobin metabolism and fecal occult blood tests. In the upper gastrointestinal tract, hemoglobin is degraded by gastric pepsin and/or pancreatic proteases in the proximal small intestine, resulting in heme and globin. Some (generally < 15%) intraluminal heme is reabsorbed in the small intestine. A portion of heme that is not absorbed is converted to porphyrins and iron via poorly understood mechanisms; this portion of heme has been termed the "intestinal converted fraction" of heme. This fraction is not detected by guaiac tests but is detected by the heme–porphyrin assay (HemoQuant), which measures both heme and porphyrins, and is therefore a highly accurate indicator of bleeding, regardless of level. Globin in the upper gastrointestinal tract is digested by pepsin and pancreatic and intestinal proteases and is thus not detected by immunochemical fecal occult blood tests. Used with permission from Rockey (1999) Occult gastrointestinal bleeding. *N. Engl. J. Med.* 341, 38–46.

Thus, guaiac-based tests are best at detecting large, more distal lesions. Fecal hemoglobin levels must exceed 10 mg/g (approximately 10 ml daily blood loss) before most guaiac tests are positive at least 50% of the time. It is important to emphasize that a number of other factors, many of which are dietary (Table III), influence guaiac test results. Another factor affecting the reactivity of guaiac-based tests is fecal rehydration, which markedly raises sensitivity but significantly reduces specificity. It is commonly believed that oral iron causes false positive guaiac tests. Care must be taken not to confuse the dark-green or black appearance of iron in stool with the typical blue color of a positive guaiac reaction; it has been confirmed that orally administered iron, even in large amounts, does not cause false positive guaiac reactions. Bismuth-containing antacids and antidiarrheals cause the stool to become black and may confound reading of guaiac-based tests, or may even cause confusion with melena.

Immunochemical tests (using antibodies directed against human globin) readily detect colonic blood and do not detect small quantities of blood from upper gastrointestinal sources (Fig. 2). Thus, they are more specific than guaiac-based tests. However, they are

TABLE III Factors Affecting Fecal Occult Blood Tests[a]

| Variable | Guaiac | Heme–porphyrin | Immunochemical |
|---|---|---|---|
| **False positives** | | | |
| Animal hemoglobin | +++ | +++ | 0 |
| Dietary peroxidases | ++ | 0 | 0 |
| **False negatives** | | | |
| Hemoglobin degradation | + | 0 | ++ |
| Storage | ++ | +++ | + |
| Vitamin C | + | 0 | 0 |

[a] Adapted with permission from Rockey (1999). Occult gastrointestinal bleeding. *N. Engl. J. Med.* 341, 38–46. Relative comparisons are shown on a scale of 0 to +, ++, +++, with 0 being negative and +++ highly positive.

limited by technical problems such as loss of hemoglobin antigenicity at room temperature and the requirement for laboratory processing. Finally, the heme–porphyrin test (HemoQuant, Mayo Medical Laboratories, Rochester, MN) measures porphyrin spectrofluorometrically and therefore allows precise determination of total stool hemoglobin. Substances that may interfere with or cause false positive guaiac tests (i.e., vegetable peroxidases) do not affect this test. However, this test detects myoglobin, an important source of nonhuman heme found in red meats. This test is the most sensitive method to detect occult gastrointestinal bleeding.

### *Differential Diagnosis and Approach to Evaluation*

Fecal occult blood tests are widely used to screen the colon for cancer, but also help to investigate symptoms. Virtually any gastrointestinal lesion can bleed and cause a positive fecal occult blood test result (Table IV). Once a patient is determined to have fecal occult blood, investigation is initially focused on the colon. However, the choice of colonic imaging modality (colonoscopic or radiographic) is controversial, both in terms of diagnostic accuracy and in terms of cost. Flexible sigmoidoscopy is necessary for patients undergoing air-contrast barium enema to fully evaluate the rectosigmoid colon. Air-contrast barium enema can accurately detect colonic malignancy and large adenomas; however, under certain circumstances, it may also be inaccurate. Colonoscopy is generally considered to be more accurate but may also miss important lesions. Computed tomography and computerized rendering of the colon (virtual colonoscopy or colonography) may eventually play a role in colon evaluation, but are currently not widely available. At present, it is generally believed that the best choice for evaluation of the colon in patients with fecal occult blood is colonoscopy.

Patients with fecal occult blood but a normal colon often harbor upper gastrointestinal pathology. A number of studies have addressed this issue and have emphasized that upper endoscopy will detect abnormalities in around one-third of patients. This finding is somewhat surprising because the guaiac-based tests used in these studies have a relatively low sensitivity for detecting upper gastrointestinal blood. Nonetheless, guaiac-based tests are clearly capable of detecting even small amounts of upper gastrointestinal tract blood, and many of the types of lesions identified in the upper gastrointestinal tract in these studies bleed enough to produce positive guaiac-based tests. The cost-effectiveness of upper gastrointestinal tract investigation in patients with fecal occult blood and normal colons is unknown.

Whether patients with occult blood found in the stool after digital rectal examination should be evaluated is controversial; anorectal trauma and/or dietary factors may lead to false positive tests. However, in both symptomatic and asymptomatic patients with fecal occult blood detected by digital rectal examination, the number of new lesions identified by gastrointestinal

**TABLE IV Differential Diagnosis of Occult Gastrointestinal Bleeding**[a]

| | |
|---|---|
| **Mass lesions** | **Vascular** |
| Carcinoma (any site)[a] | Vascular ectasia (any site)[b] |
| Large (>1.5 cm) adenoma (any site) | Portal hypertensive gastropathy/colopathy |
| **Inflammation** | Watermelon stomach |
| Erosive esophagitis[b] | Hemangioma |
| Ulcer (any site)[b] | Dieulafoy's ulcer[d] |
| Cameron lesions[c] | **Infectious** |
| Erosive gastritis | Hookworm |
| Celiac sprue | Whipworm |
| Ulcerative colitis | Strongyloidiasis |
| Crohn's disease | Ascariasis |
| Colitis (nonspecific) | Tuberculous enterocolitis |
| Idiopathic cecal ulcer | Amebiasis |
| **Miscellaneous** | **Surreptitious** |
| Long-distance running | Hemoptysis |
| Factitious | Oropharyngeal (including epistaxis) |
| | Pancreaticobiliary |

[a] Adapted with permission from Rockey (1999). Occult gastrointestinal bleeding. *N. Engl. J. Med.* 341, 38–46. Potential lesions leading to fecal occult blood or iron deficiency anemia are shown. Lesions that may lead to recurrent obscure bleeding are not listed (see Table I).

[b] Most common abnormalities.

[c] Linear erosions within a hiatus hernia.

[d] Large superficial artery underlying mucosal defect.

evaluation is substantial and therefore evaluation is indicated; if symptoms are present, further evaluation should be directed accordingly. Whether testing stool obtained by digital rectal examination is a viable cancer screening option is an important question and would be influenced by variables such as improved compliance versus inadequate dietary preparation.

Occult gastrointestinal bleeding generally should not be attributed to anticoagulant or aspirin therapy. Indeed, fecal blood levels in patients therapeutically anticoagulated have been reported to be normal and low-dose aspirin alone does not result in significantly elevated fecal blood levels. Further, neither warfarin nor low-dose aspirin alone appears to cause positive guaiac-based fecal occult blood tests. Thus, a positive fecal occult blood test should not be attributed to the effect of anticoagulation or aspirin alone, but rather should lead to standard evaluation.

### *Treatment and Outcome*

Treatment of patients with fecal occult blood varies and depends on the abnormalities identified. Likewise, outcomes are directly related to specific findings. Non-steroidal antiinflammatory drugs cause mucosal injury and should be discontinued if possible. Patients with vascular ectasias are problematic, and if they bleed chronically should be managed carefully (see earlier discussion of obscure gastrointestinal bleeding). The prognosis of patients with positive fecal occult blood tests but no identifiable gastrointestinal pathology is generally favorable, but long-term outcome data on this subject are lacking.

## Iron Deficiency Anemia

Iron deficiency anemia is the most common form of anemia in the world. In the United States, 5–11% of adult females and 1–4% of adult males are iron deficient whereas approximately 5 and 2% of adult women and men, respectively, have iron deficiency anemia. Although iron deficiency anemia in women of reproductive age is typically assigned to menstrual- and pregnancy-associated iron losses, in groups other than premenopausal women, iron deficiency anemia is assumed to be due to chronic occult gastrointestinal bleeding, resulting depletion of the iron pool and ultimately anemia (Fig. 3).

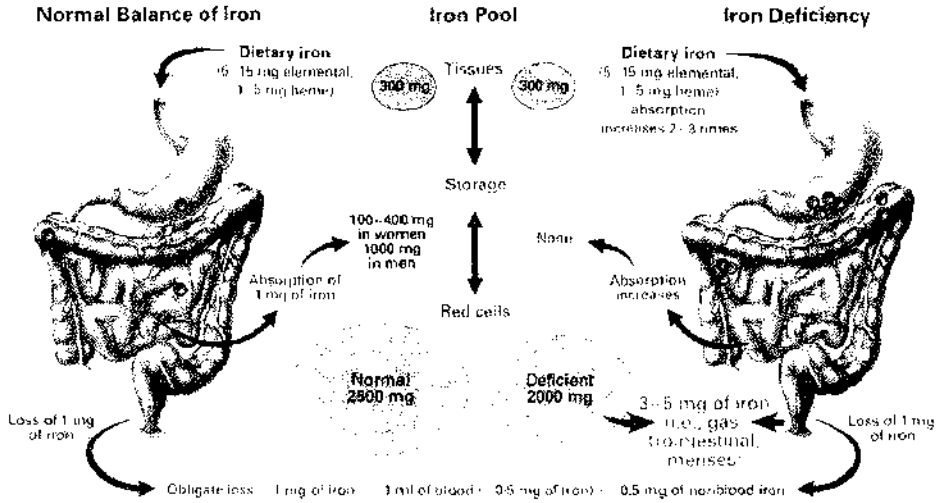


FIGURE 3 Gastrointestinal blood loss and iron balance. Normal obligate daily iron loss is from (1) blood loss (presumably from gastrointestinal mucosal microerosions or microulcerations) and (2) iron in sloughed gut epithelial cells. Total daily iron loss is thus approximately 1 mg. The usual Western diet contains mostly elemental iron, of which about 10% is absorbed. Heme-iron, derived primarily from myoglobin in meats, is preferentially absorbed and accounts for 60–80% of the iron absorbed per day. Under normal circumstances, iron homeostasis is tightly regulated and daily iron loss is precisely balanced by iron absorption. Iron deficiency results only when the dynamic, but limited, absorptive capacity of the small intestine is exceeded by iron loss. The time required to develop iron deficiency depends on the size of initial iron stores, the rate of bleeding, and intestinal iron absorption. Iron deficiency generally occurs only with increased loss of over 5 ml of blood daily. Importantly, anemia is a late manifestation of the iron-depleted state. With permission from Rockey (1999). Occult gastrointestinal bleeding. *N. Engl. J. Med.* 341, 38–46

### *Differential Diagnosis and Approach to Evaluation*

The diagnosis of iron deficiency and iron deficiency anemia is most often confirmed by a low serum ferritin level or a bone marrow examination. Effort should be made to verify the diagnosis in equivocal cases, because a diagnosis of iron deficiency anemia leads to extensive and often costly evaluation. Iron deficiency without anemia is often also associated with significant gastrointestinal tract abnormalities.

As with all occult gastrointestinal bleeding, virtually any gastrointestinal tract lesion can bleed in an occult fashion and lead to iron deficiency anemia (Table IV). Although the colon is traditionally viewed as the source of bleeding in most patients with iron deficiency anemia, a number of studies have now documented prominent abnormalities in the upper gastrointestinal tract in patients without colonic lesions. The most common abnormalities have been erosive disease of the esophagus, stomach, and duodenum (i.e., severe esophagitis, presumably reflux mediated, gastric, or duodenal ulcer). Colon cancers and large adenomas are the most commonly identified lesions in the colon. Importantly, only about 5% of patients have had simultaneous pathology identified in both upper and lower gastrointestinal sites.

A large body of literature has helped change the way patients with iron deficiency anemia are currently managed. The emphasis is on the importance of evaluation of the upper gastrointestinal tract. It is important to emphasize that although mass lesions and large ulcerative upper gastrointestinal lesions can lead to significant blood loss (up to 20 ml/day), it is unlikely that trivial lesions such as mild inflammation and small adenomas bleed enough to lead to iron deficiency. Thus, care must be taken when attributing iron deficiency anemia to lesions not expected to cause significant bleeding.

Gastrointestinal symptoms in patients with iron deficiency anemia typically help focus gastrointestinal tract evaluation. Directed gastrointestinal tract evaluation is practical and desirable as a cost- and risk-containing strategy. Although many patients with iron deficiency anemia are entirely asymptomatic, those with classic symptoms (change in stool caliber, epigastric pain, or heartburn) should undergo site-directed investigation. The initial investigation should be directed toward the location of specific symptoms, if present (Fig. 4). Because dual lesions are rare, identification of an abnormality clearly consistent with bleeding (mass lesion, large ulceration, severe inflammation) makes further evaluation unnecessary. In the absence of symptoms, particularly in elderly patients, evaluation should

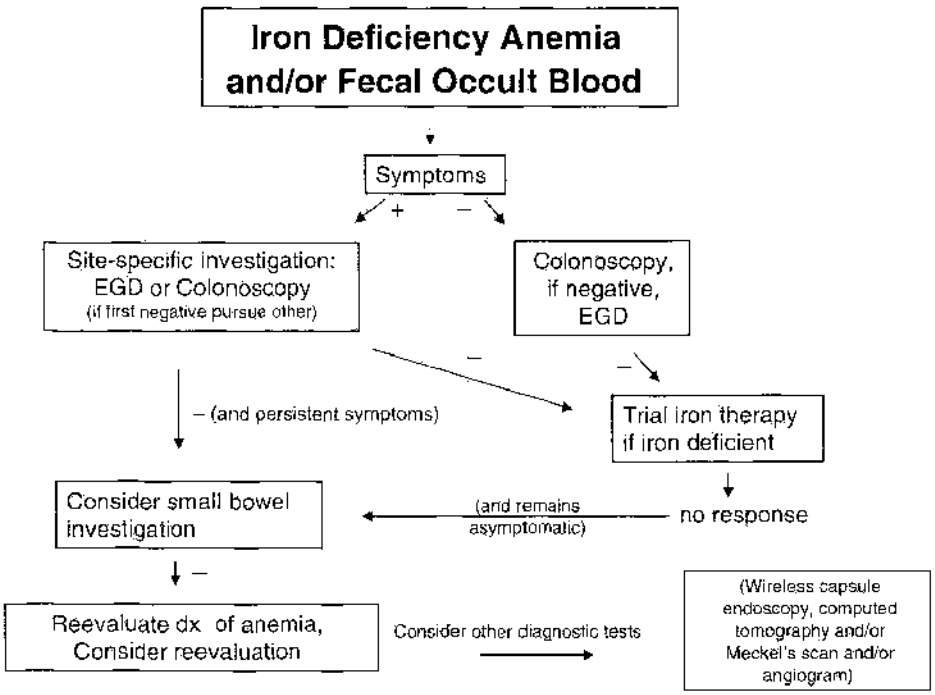


FIGURE 4 Scheme for evaluation of fecal occult blood and iron deficiency anemia. EGD, Esophagogastroduodenoscopy. From Rockey, D. C. (2002). Gastrointestinal bleeding. *In* "Sleisenger & Fordtran's Gastrointestinal and Liver Disease" (M. Feldman *et al.*, eds.), 7th Ed. W. B. Saunders, Philadelphia). Used with permission.

begin with the colon, but if this is negative, evaluation of the upper gastrointestinal tract is indicated.

The degree of gastrointestinal evaluation in premenopausal women with iron deficiency anemia is controversial. On one hand, few iron deficiency anemia premenopausal women undergo evaluation. However, in studies focusing on those referred to gastroenterologists, it has been reported that up to 20% of patients will have significant gastrointestinal tract abnormalities, including important lesions such as colon cancer, celiac sprue, and inflammatory bowel disease. Clearly, a management algorithm is required for these patients. A practical approach is as follows: for those with specific gastrointestinal symptoms, weight loss, fecal occult blood, or perhaps severe anemia, evaluation is indicated. For asymptomatic women or those with abnormal menses, whether to pursue gastrointestinal tract evaluation should be individualized.

The small bowel is an important potential site of bleeding in patients with negative colon and upper gastrointestinal tract examinations. For example, celiac sprue, a classic small bowel disorder, can not only lead to malabsorption of iron, but may cause occult bleeding and should be considered. This is especially true in patients of Northern European descent. Radiographic examination of the small bowel (enteroclysis or small bowel follow-through) is of limited value and is generally not recommended. On the other hand, push enteroscopy has a greater sensitivity for mucosal abnormalities and detects abnormalities in approximately 25% of patients. However, it remains unknown whether push enteroscopy leads to improved outcomes. Likewise, the use of wireless capsule endoscopy in patients with iron deficiency anemia remains unsettled.

Nearly one-third of patients with iron deficiency anemia have no identifiable gastrointestinal tract abnormality by routine endoscopic examination. In these patients, explanations for iron deficiency anemia include non-gastrointestinal blood loss, misdiagnosis of the type of anemia, missed lesions, or nutritional deficiency. Additionally, these patients may have gastric achlorhydria and atrophy, suggesting that lack of acid in this subgroup could contribute to iron malabsorption.

### *Treatment and Outcome*

All patients with iron deficiency anemia should be started on iron therapy. Oral ferrous sulfate is the best option because it is inexpensive and effective (the recommended dose is 300 mg three times daily). Intolerance to ferrous sulfate is common; in these patients, ferrous gluconate and fumarate are acceptable alternatives. Parenteral iron therapy is reserved only for patients with severe malabsorption or intolerance to all iron supplements. The prognosis for patients with iron deficiency anemia and readily treatable lesions (i.e., duodenal ulcer, esophagitis, large adenoma) is excellent. Likewise, the prognosis for patients who do not have lesions identified during gastrointestinal evaluation is favorable; long-term followup of patients in this group suggests that significant lesions do not surface at a later date. In patients who do not respond to iron therapy, the diagnosis of iron deficiency anemia should be reevaluated and repeat gastrointestinal evaluation should be contemplated. A careful reexamination of the gastrointestinal tract for easily missed lesions (in the esophagus, for Cameron lesions within hiatus hernia; in the stomach, for atrophic gastritis; in the small bowel, celiac sprue) is indicated when evaluating persistent unexplained iron deficiency anemia.

## CONCLUSIONS

Occult gastrointestinal bleeding is most often manifest as occult blood in the stool, typically by the use of guaiac-based fecal occult blood tests. Occult gastrointestinal bleeding may also be manifest as iron deficiency anemia, which often results from chronic occult gastrointestinal bleeding. These forms of occult gastrointestinal bleeding are common. In contrast to fecal occult blood and iron deficiency anemia, obscure gastrointestinal bleeding is uncommon but represents a considerable diagnostic and therapeutic challenge. Evaluation of patients with fecal occult blood and iron deficiency anemia often parallels similar algorithms and in asymptomatic patients should usually begin with investigation of the colon. Colonoscopy is the preferred method, but flexible sigmoidoscopy plus air-contrast barium enema may be acceptable. If evaluation of the colon does not reveal a bleeding site, evaluation of the upper gastrointestinal tract should be considered, and in patiens with iron deficiency anemia, this is mandatory. In patients with iron deficiency anemia, the role of small bowel investigation is controversial and is probably best reserved for those with persistent gastrointestinal symptoms or those who fail to respond to appropriate therapy. Celiac sprue should be considered as a potential cause of iron deficiency anemia in certain epidemiological groups. The treatment and prognosis of patiens with occult blood in the stool and/or iron deficiency anemia depends on the gastrointestinal tract abnormalities identified. Those without identifiable bleeding sits generally respond to conservative management and have a favorable prognosis. For patients with obscure gastrointestinal bleeding, investigation is typicaly focused on the small bowel, typically with enteroscopy.

but perhaps also with wireless capsule endoscopy. In these patients, vascular ectasias are a major consideration. The prognosis for these patients is less clear, and outcome studies are required. This group requires a committed and experienced team approach to diagnosis and therapy.

## Acknowledgment

This work was supported by the Burroughs Wellcome Fund (BWF Clinical Scientist Award).

## See Also the Following Articles

**Colonoscopy • Endoscopy, Complications of • Hemobilia • Hemorrhage • Lower Gastrointestinal Bleeding and Severe Hematochezia • Meckel's Diverticulum • Sigmoidoscopy • Trauma, Overview • Upper Gastrointestinal Bleeding • Variceal Bleeding**

## Further Reading

Ahlquist, D. A., McGill, D. B., Schwartz, S., Taylor, W. F., and Owen, R. A. (1985). Fecal blood levels in health and disease. A study using HemoQuant. *N. Engl. J. Med.* **312**, 1422–1428.

Ahlquist, D. A., McGill, D. B., Fleming, J. L., *et al.* (1989). Patterns of occult bleeding in asymptomatic colorectal cancer. *Cancer* **63**, 1826–1830.

Appleyard, M., Fireman, Z., Glukhovsky, A., *et al.* (2000). A randomized trial comparing wireless capsule endoscopy with push enteroscopy for the detection of small-bowel lesions. *Gastroenterology* **119**, 1431–1438.

Bloomfeld, R. S., Smith, T. P., Schneider, A. M., and Rockey, D. C. (2000). Provocative angiography in patients with gastrointestinal hemorrhage of obscure origin. *Am. J. Gastroenterol.* **95**, 2807–2812.

Chak, A., Koehler, M. K., Sundaram, S. N., Cooper, G. S., Canto, M. I., and Sivak, M. V., Jr. (1998). Diagnostic and therapeutic impact of push enteroscopy: Analysis of factors associated with positive findings. *Gastrointest. Endosc.* **47**, 18–22.

Chalasani, N., Clark, W. S., and Wilcox, C. M. (1997). Blood urea nitrogen to creatinine concentration in gastrointestinal bleeding: A reappraisal [see comments]. *Am. J. Gastroenterol.* **92**, 1796–1799.

Foutch, P. G., Rex, D. K., and Lieberman, D. A. (1995). Prevalence and natural history of colonic angiodysplasia among healthy asymptomatic people. *Am. J. Gastroenterol.* **90**, 564–567.

Hara, A. K., Johnson, C. D., Reed, J. E., *et al.* (1997). Detection of colorectal polyps with CT colography: Initial assessment of sensitivity and specificity. *Radiology* **205**, 59–65.

Iddan, G., Meron, G., Glukhovsky, A., and Swain, P. (2000). Wireless capsule endoscopy. *Nature* **405**, 417.

Lewis, B. S. (1994). Small intestinal bleeding. *Gastroenterol. Clin. North Am.* **23**, 67–91.

Rockey, D. C. (1999). Occult gastrointestinal bleeding. *N. Engl. J. Med.* **341**, 38–46.

Rockey, D. C. (2002). Gastrointestinal bleeding. In "Sleisenger & Fordtran's Gastrointestinal and Liver Disease" (M. Feldman *et al.*, eds.), 7th Ed. W. B. Saunders, Philadelphia, PA.

Rockey, D. C., and Cello, J. P. (1993). Evaluation of the gastrointestinal tract in patients with iron deficiency anemia. *N. Engl. J. Med.* **329**, 1691–1695.

Rockey, D. C., Koch, J., Cello, J. P., Sanders, L. L., and McQuaid, K. (1998). Relative frequency of upper gastrointestinal and colonic lesions in patients with positive fecal occult-blood tests. *N. Engl. J. Med.* **339**, 153–159.

van Cutsem, E., Rutgeerts, P., and Vantrappen, G. (1990). Treatment of bleeding gastrointestinal vascular malformations with oestrogen-progesterone. *Lancet* **335**, 953–955.

Waye, J. D. (1997). Enteroscopy. *Gastrointest. Endosc.* **46**, 247–256.

Winawer, S. J., Stewart, E. T., Zauber, A. G., *et al.* (2000). A comparison of colonoscopy and double-contrast barium enema for surveillance after polypectomy. National Polyp Study Work Group. *N. Engl. J. Med.* **342**, 1766–1772.

Zuckerman, G. R., Prakash, C., Askin, M. P., and Lewis, B. S. (2000). AGA technical review on the evaluation and management of occult and obscure gastrointestinal bleeding. *Gastroenterology* **118**, 201–221.

# Over-the-Counter Drugs

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**acid-neutralizing capacity** Amount of acid (mEq) neutralized by a unit dose (teaspoonful or tablet) of an antacid.

**antacids** Soluble and/or insoluble substances capable of buffering or neutralizing gastric (stomach) acid.

**antiflatulents** Drugs effective for the relief of painful bloating or sensations of pressure and fullness, commonly referred to as gas in the digestive tract.

**constipation** Commonly defined as related to decreased bowel movement frequency, difficulty in initiating passage of feces, passage of firm or small-volume feces, or a feeling of incomplete evacuation.

**diarrhea** Symptom of several gastrointestinal disorders affecting water and electrolyte transport; characterized by alteration of the frequency and consistency of stools.

**dyspepsia** Mild pain present in the upper abdomen.

**heartburn** Specific symptom of gastroesophageal reflux disease, typically manifested by a burning sensation in the upper abdomen, behind the chest, and as high as the throat.

**histamine-2 (H2) receptor antagonists** Drugs that block action of histamine at a specific histamine (type 2) receptor located in the stomach, which results in effective inhibition of gastric acid secretion.

**Increasing numbers of drugs are obtainable without a prescription, i.e., over the counter (OTC), for self-treatment of mild gastrointestinal symptoms. The consumer must be able to recognize the symptoms of the condition that the product can treat easily, without medical assistance. Unlike prescription-based drugs, the ingestion of which requires physicians' supervision and management for treating the underlying disease process, OTC drugs are primarily used for self-treatment of well-recognized symptoms by consumers. It is increasingly important to review the therapeutics of gastrointestinal drugs specifically available for self-use and to remain vigilant about the safe use of drugs sold on an OTC basis in the United States.**

## INTRODUCTION

The availability of OTC drugs lessens the economic burden to our health care system and clearly provides much needed convenience to consumers. However, despite these advantages, there are clear risks related to the use of OTC drugs. For example, aspirin and acetaminophen are still associated with serious gastrointestinal toxicity despite their availability as OTC drugs for many years. In addition, chronic use of antacids and OTC gastric antisecretory drugs can delay the diagnosis of gastric cancer. Therefore, it is most essential that consumers are made aware of the indications and limitations of OTC drugs through improved education by the pharmaceutical manufacturers and easily understood labels, affixed to the containers, which should explain the desired uses, treatment duration, dosage, and adverse effects of these drugs. Clear drug labeling, as mandated by the Food and Drug Administration (FDA), and perhaps pharmacist counseling are most essential for the safe use of OTC drugs.

## AGENTS BUFFERING OR INHIBITING GASTRIC ACIDITY

### Antacids

Antacids are drugs capable of buffering stomach acid. Antacids raise the pH of the stomach contents toward neutrality. An antacid that raises the pH from 1.5 to 3.5 produces a 100-fold reduction in the concentration of gastric acid. Furthermore, the reduction of acidity is accompanied by inhibition of pepsin activity, another important component of the digestive juice. According to their approved labeling, the only symptoms that can be safely diagnosed and self-treated with OTC antacids are those caused by excess stomach acid. These symptoms have been described as burning sensations in the upper abdomen, behind the chest, and high as the throat. The official FDA-approved claims for antacids are for the relief of "heartburn, sour stomach, acid indigestion, and upset stomach." Based on the many years that OTC antacids have been used for heartburn, it is apparent that a consumer who has heartburn can determine when he or she has heartburn, and in most cases can predict what foods, situations, or life stresses can cause heartburn.

Great disparity exists in the acid-neutralizing capacity (ANC) of various antacids (Table I). The more

 

TABLE 1 Acid-Neutralizing Capacity of Selected Antacids[a]

| Product | Acid-neutralizing capacity in mEq acid/dose | Standard dose to neutralize 152 mEq acid/dose |
|---|---|---|
| Alka-Seltzer (tablet) | 10.6 tablets | 15 tablets |
| Amphogel (liquid) | 6.5 tsp | 25 tsp |
| Amphogel (tablet) | 9 tablets | 17 tablets |
| Maalox (liquid) | 13.5 tsp | 11 tsp |
| Maalox Therapeutic Concentrate (liquid) | 28.5 tsp | 5 tsp |
| Mylanta (liquid) | 12.5 tsp | 12 tsp |
| Mylanta II (liquid) | 25.5 tsp | 6 tsp |
| Mylanta II (tablet) | 23 tablets | 7 tablets |
| Titralac (liquid) | 19 tsp | 8 tsp |
| Tums (tablet) | 10 tablets | 16 tablets |

[a]The amount of acid (mEq) being neutralized by a unit dose (teaspoonful or tablet) of an antacid; tsp, teaspoonful.

*Note:* Data adapted from Zimmerman, 1983.

potent antacids (e.g., Mylanta II) require a smaller dose, compared to a weaker product (e.g., Amphogel), and this is advantageous for treating ulcers. However, ulcer treatment is clearly outside the scope of OTC product labeling and should be treated only by physicians, not by self-treatment. The dose of antacid that will relieve pain in a patient with gastric ulcer must provide an ANC of 152 mEq. A weaker product, such as Amphogel, would require 25 teaspoonfuls to neutralize gastric acid, whereas a stronger product, such as Mylanta II, requires only 6 teaspoonfuls (Table 1).

It should be noted that liquid antacid preparations generally provide faster buffering action than do tablet preparations. However, from a therapeutic perspective, there is a dissociation between the duration of buffering capacity of antacids, which is relatively short (30 minutes), and the duration of the pain relief required for heartburn or peptic ulcer (approximately 4 hours). Thus, on the basis of pain relief, antacids administered at a low frequency of about three times daily would not be therapeutically sufficient for healing gastric or duodenal ulcers. However, this low frequency of administration does provides pain relief in mild to moderate heartburn.

The neutralization of gastric contents by antacids promotes antral gastrin release, which promotes gastric emptying and hence contributes to the short duration of their buffering action. Due to the gastrin-induced gastric emptying, the more potent antacids have durations of buffering action essentially similar to those of weaker antacids. Therefore, the increased potency of an antacid should not be a criterion for a patient's product selection for the self-treatment of heartburn.

Several principal ingredients are present in antacids: bicarbonate (sodium, potassium, and calcium), aluminum, magnesium, phosphate, and silicates. Bismuth subsalicylate (Pepto-Bismol), which is marketed for the treatment of heartburn, has minimal antacid action and therefore is not pharmacologically classified as an antacid. All antacid products contain at least one ingredient; most contain at least two ingredients. Sodium bicarbonate and calcium carbonate are more potent antacids, compared to magnesium compounds. Magnesium compounds are more potent than aluminum compounds. Sodium and potassium bicarbonate are soluble antacids that are readily absorbed into the blood, and thus are particularly risky for patients with impaired kidney function. Calcium compounds (calcium carbonate and calcium phosphate) are potent and fast-acting antacids that are readily absorbed. However, these drugs may form calcium kidney stones. Paradoxically, calcium antacids promote antral gastrin release to a greater degree than do noncalcium antacids, which in turn stimulate gastric acid production. The aluminum compounds induce constipation and the magnesium compounds induce diarrhea, thus these two ingredients are combined together, although the net effect of the combined product is laxation. This is especially noted when the combined drugs are taken at increased dosages. The silicate antacids (e.g., magnesium trisilicate) interfere with the absorption of some drugs and this needs to be considered by patients and health care providers. For specific details about all available antacid products and their pharmacological characteristics, the readers are encouraged to consult the *Physicians' Desk Reference for Nonprescription Drugs*.

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TABLE II Pharmacological Characteristics of Selected OTC Histamine-2 Receptor Antagonists

| Drug | Trade name | Doses | Half-life (hours) | Drug interactions |
|---|---|---|---|---|
| Cimetidine | Tagamet HB 200, others | 200 mg up to twice daily | 2.0 | Yes[a] |
| Ranitidine | Zantac 75, others | 75 mg up to twice daily | 2.1 | No |
| Famotidine | Pepcid AC | 10 mg up to twice daily | 2.6 | No |

[a] The OTC dosage of cimetidine has a small potential for pharmacokinetic interaction with theophylline. Prescription dosage of cimetidine has shown pharmacokinetic interactions with phenytoin, theophylline, and warfarin.

### Histamine-2 Receptor Antagonists

Histamine-2 (H2) receptor antagonists were previously marketed as prescription-based products for the healing and prevention of gastric ulcers and duodenal ulcers, and for the management of gastroesophageal reflux disease (GERD) due to their well-known gastric antisecretory actions. However, patients with GERD represent a spectrum ranging from mild to severe disease states and many patients with heartburn symptoms have been accustomed to the use of OTC antacids and H2 receptor antagonists. Therefore, three of the four H2 receptor antagonists that were previously marketed as prescription-based products were switched to OTC use at reduced doses, which are one-half of their prescription doses (Table II). The currently available OTC drugs, cimetidine, ranitidine, and famotidine, have essentially two similar medical claims in their labeling: (a) "for the relief of heartburn associated with acid indigestion and sour stomach" and (b) "for the prevention of heartburn associated with acid indigestion and sour stomach brought on by certain foods or beverages." The H2 antagonist nizatidine, which is currently available as a prescription-based product, has not yet been switched to an OTC status.

The frequency of the administration of all three H2 antagonists is one to two doses per day and the duration of self-use should not exceed 2 continuous weeks, except under the advice and supervision of a physician. All three drugs have similar biological half-lives of about 2 hours (Table II). However, as is the case with prescription-based products, ranitidine and famotidine, but not cimetidine, are marketed at doses that exceed their median effective gastric antisecretory doses ($ED_{50}$). Thus, when administered at the recommended OTC dosage of twice daily, it is expected that ranitidine and famotidine would provide a much longer duration of gastric antisecretory action than would cimetidine. However, despite the differences in the magnitude of their doses, all three drugs appear to have similar degree of efficacy for the treatment and prevention of heartburn.

Unlike antacids, which provide immediate relief of heartburn, there is some delay (15–30 minutes) in the onset of pain relief provided by H2 antagonists, because they are systemically acting drugs and require absorption into the bloodstream. However, one H2 antagonist combines famotidine with the antacids calcium carbonate and magnesium hydroxide (Pepcid Complete) to provide both immediate and prolonged gastric antisecretory action.

The tolerability of the three drugs appears to be similar. However, given the fact that cimetidine is known to inhibit various P450-metabolizing isoenzymes, which could affect metabolism of other drugs and thereby increase their blood concentration, patients should consult with their physicians if they are taking theophylline, warfarin, and phenytoin with cimetidine.

## ANTIFLATULENT (ANTIGAS) AGENTS

An antiflatulent is a drug that expels gas from the stomach and intestines. Simethicone (contained in products such as Mylicon, Phazyme, GAS-X, Gas Aid, and others) is the only drug approved as antiflatulent by the FDA. The drug reduces the surface tension of small gas bubbles and is often combined with antacids. The approved OTC indication for the product is "for the relief of painful bloating, and the sensation of pressure and fullness, commonly referred to as gas in the digestive tract." Such gas is frequently caused by excessive swallowing of air or by eating certain foods. The antiflatulent property is useful in conditions in which the retention of gas may be problematic, such as air swallowing, functional dyspepsia, postoperative gaseous distension, peptic ulcers, spastic or irritable colon, or diverticulosis. Tablet or liquid formulations of the drug are used in dosages of 80 to 125 mg, six times daily after meals and at bedtime, or as directed by a physician.

## ANTIDIARRHEAL AGENTS

Diarrhea is well recognized by ordinary individuals to be a disorder of "too rapid evacuation of too fluid stools." Diarrhea is a symptom of several gastrointestinal (GI) diseases affecting water and electrolyte transport. Several types of drugs exist for the treatment of diarrhea,

In some situations, diarrhea is an adaptive and defensive process that expedites the removal of toxins, bacteria, fungi, viruses, and protozoa from the GI tract. Under these conditions, it is probably best not to interfere with their removal using an antidiarrheal drug, because this might prolong disease. Moreover, antidiarrheal drugs do not affect the underlying GI disease process, but rather provide control of symptoms.

## Antipropulsive Drugs

Loperamide hydrochloride (e.g., Imodium A-D) was previously available only as a prescription-based drug; after about 10 years, it was introduced for OTC use. Loperamide is the only available OTC antidiarrheal drug; it works by inhibiting intestinal propulsive activity and by affecting water and electrolyte transport by the bowel, probably secondary to the inhibition of propulsive motility. Loperamide is an opiate receptor agonist similar to morphine and specifically binds to receptors in the brain and in the gut (myenteric plexus). Loperamide stimulates intestinal circular muscle contractile activity to induce segmentation or mixing, but, unlike morphine, it has reduced ability to cross the blood–brain barrier.

Loperamide is indicated for the symptomatic relief of acute nonspecific diarrhea and should not be used if diarrhea is accompanied by high fever (greater than 101°F), or if blood is present in the stool, suggesting an infectious etiology. The dosage for adults is 4 mg (two caplets or four teaspoonfuls) after the first loose bowel movement. If needed, 2 mg can be used after each additional loose bowel movement. An adult should not exceed a total of 8 mg in a 24-hour period unless directed by a physician. A lower dosage is recommended for children. Warnings appear on the package label and instruct the user not to take the drug for more than 2 days unless directed by a physician. Following systemic absorption, loperamide has a long half-life of 18 hours, and the recommended dosage must therefore be adhered to in order to avoid potential toxicity.

Overdose of loperamide may result in constipation, central nervous system depression, and nausea. A slurry of activated charcoal administered promptly after ingestion may reduce the amount of the drug that is absorbed. In the event of overdosage, patients should be monitored for signs of central nervous system (CNS) depression for at least 24 hours. In addition, children may be more sensitive to the CNS effect of loperamide. If CNS depression is observed, the opiate antagonist naloxone should be used. If responsive to nalaxone, vital signs must be monitored carefully for the recurrence of symptoms of drug overdose for at least 24 hours after the last dose of naloxone.

## Bismuth Drugs

Bismuth subsalicylate (Pepto-Bismol) is the only colloidal bismuth salt drug approved for OTC use in multiple GI conditions, including "diarrhea, heartburn, indigestion without constipation, nausea, and upset stomach." The mechanism of action of bismuth subsalicylate in these gastrointestinal disorders is not completely understood. Although colloidal bismuth compounds have no significant acid-neutralizing capacity, they inhibit the action of pepsin, increase the secretion of mucus, and interact with protein in necrotic ulcer craters, presumably forming a barrier to the diffusion of acid. Bismuth colloids have an antibacterial action, which is relevant for the treatment of infectious diarrhea and peptic ulcers (e.g., *Helicobacter pylori*). The salicylate component of bismuth subsalicylate may exert intestinal antiinflammatory and antisecretory actions. Thus, the combined antibacterial and intestinal antisecretory action of bismuth subsalicylate is relevant for the OTC treatment of mild to moderate diarrhea. Pepto-Bismol controls diarrhea within 24 hours, and also relieves associated abdominal cramps.

Pepto-Bismol is available in two liquid suspension forms (262 and 525 mg per 15 ml) and in a tablet dosage form (102 mg per tablet). The recommended dosage for adults is 262 to 1050 mg, to be repeated every hour, if needed, to a maximum of four doses in 24-hour period. Lower dosages are provided for children of various age groups. Pepto-Bismol should not be used in patients who have a known allergy to aspirin. Caution is also advised when administering to patients taking medications for anticoagulation, diabetes, and gout. A warning statement advises caution in the administration of the drug to children, including teenagers, during or after recovery from chicken pox or flu. In addition, the medication may cause a temporary and harmless darkening of the tongue and/or stool.

## Adsorbent Drugs

Adsorbents have been so named because of their potential to adsorb intestinal luminal toxins and bacteria associated with some types of infectious diarrhea, and theoretically they should enhance fecal elimination of the toxins or bacteria. Although this adsorption principle has been demonstrated in *in vitro* studies, there have been no meaningful confirmatory *in vivo* studies. Furthermore, adsorbents are of little or no value for the treatment or prevention of acute infectious diarrhea. Clearly, additional clinical studies are needed to

support the utility of these drugs for the treatment of diarrhea. Several types of adsorbent drugs are commercially available for OTC use and include kaolin (e.g., Kaopectate, Donagel), attapulgite (e.g., Diasorb, Rheaban), and pectin (e.g., Kaopectate, Donagel). The official claim for these products is "for the relief of diarrhea and cramps."

### Oral Rehydration Therapy

Although healthy adults with episodes of mild to moderate diarrhea do not need extensive oral hydration therapy, they are advised to eat easily digested food and to drink noncarbonated beverages such as fruit juices. Fruit juices contain easily digested sugars and water. It is well established that glucose promotes the intestinal absorption of water, sodium, and other electrolytes, thus overcoming the losses associated with diarrhea. In patients with severe diarrhea, however, and especially young children, the use of oral hydration solutions containing glucose, electrolytes, and amino acids in proportions similar to the World Health Organization formula is advised. Such solutions are available OTC for use in infants and children when recommended by physicians (e.g., Pedialyte).

## LAXATIVES

Laxatives are drugs or fibers that relieve the symptoms of constipation. Constipation is understood by lay individuals to be related to decreased fecal frequency, difficulty in initiating fecal passage, the passage of firm or small-volume feces, or a feeling of incomplete evacuation. Although there are several types of laxatives, most laxatives increase intestinal water content via distinct pharmacological mechanisms (summarized in Table III). All laxatives have a general warning statement that they should not be used if abdominal pain, nausea, or vomiting is present.

TABLE III Pharmacological Classifications of Major Drugs Used for the Treatment of Constipation

| Pharmacological class | Drug examples |
|---|---|
| Bulk-forming agents | Hydrophillic colloids, fibers |
| Osmotic agents | Nonabsorbable magnesium salts |
| Emollient agents | Mineral oil |
| Nonspecific stimulants or irritants | Docusate salts, anthraquinone (senna, cascara, aloe), diphenylmethane (bisacodyl), castor oil |

### Bulk-Producing Laxatives

Bulk-forming hydrophilic colloids such as psyllium husk derived from the plantago seed (e.g., Metamucil), methylcellulose (e.g., Citrucel), and calcium polycarbophil (Fibercon) are most popular with consumers. Psyllium is one of the oldest bulk laxatives, with more than 70 years of clinical application. Psyllium is available in various oral dosage forms, including powder and cookies. The bulking effect of the psyllium husk is due both to the water-holding capacity (gel formation) of the undigested fibers and to an increased bacterial mass following extensive colonic bacterial fermentation (about 85%) of the undigested fibers. Colonic fermentation of undigested psyllium fibers and other natural dietary fibers leads to the formation of short-chain fatty acids, which are osmotically active and add water to the bulk of the stools. This fermentation results in the formation of intestinal gases, which some individuals may find objectionable. However, with dose adjustments, most individuals are able to tolerate chronic treatment with psyllium and other natural dietary fibers. In contrast, the synthetic bulk laxatives methylcellulose and calcium polycarbophil act to increase colonic water content primarily by gel formation, because they are poorly fermentable (15%).

All bulk laxatives produce bowel movements after 12 to 72 hours, and are well tolerated with good safety records. Furthermore, the approved labeling indications for Metamucil (3.4 g psyllium/dose) and Citrucel (2 g/dose) are rather broad, and include the treatment of occasional constipation and, when recommended by a physician, chronic constipation and constipation associated with irritable bowel syndrome, diverticulosis, hemorrhoids, convalescence, senility, and pregnancy. In contrast, the approved labeling for calcium polycarbophil (625 mg/dose) is more limited to "the relief of constipation and to help restore and maintain regularity."

### Osmotically Active Agents (Saline Laxatives)

This group contains the drugs magnesium hydroxide (e.g., Phillips Milk of Magnesia, others), magnesium sulfate, magnesium citrate (e.g., Citrate of Magnesia), and sodium biphosphate (e.g., Fleet Phospho-Soda, Fleet Enema). Their cathartic action results from osmotically mediated water retention in the bowel. The increased intestinal volume stimulates intestinal peristalsis and promotes defecation. The magnesium-containing cathartics stimulate release of the intestinal hormone cholecystokinin, which promotes intestinal secretion and increased intestinal motility. The usual adult dose of magnesium hydroxide is 800 to 1600 mg at bedtime, which produces a bowel movement

within 6 hours. Phosphate salts are better absorbed than are magnesium salts and therefore require higher dosage to effect catharsis. Saline cathartics should not be used for more than 1 week unless directed by a physician. Both magnesium- and phosphate-containing preparations are reasonably well tolerated, but they need to be used with caution in patients with renal insufficiency or cardiac disease.

### Emollient Laxatives

Mineral oil is the only drug available as an indigestible emollient. When used for 2 to 3 days, mineral oil (e.g., Fleet Mineral Oil Enema, 118 ml/dose; or as an oral liquid) can soften very dry stools. However, its poor taste and possible oil leakage from the anus precludes its regular use. Furthermore, the chronic use of mineral oil could result in foreign body reactions and interference with the absorption of fat-soluble substances, such as some vitamins.

### Nonspecific Stimulants (Irritant Laxatives)

Stimulant laxatives induce bowel movement by virtue of their ability to alter intestinal mucosal permeability and stimulate intestinal water and electrolyte secretion in the bowel. This pharmacological class of drugs constitutes four distinct subgroups:

1. Surfactants: Anionic surfactants containing the docusate salts dioctyl sodium sulfosuccinate or dioctyl calcium sulfosuccinate (e.g., Surfak Liqui-Gels, Colace, Doxinate) are mild stimulant laxatives. These surfactants were initially believed to act by lowering the surface tension of stool to allow mixing of aqueous and fatty substances in the stool, thereby permitting easier defecation. However, more recent evidence indicates that these drugs act in a manner similar to that of other stimulant drugs in this class, by stimulating intestinal water and electrolyte secretion. However, despite their widespread use, these surfactants have marginal, if any, efficacy in most cases of constipation.

2. Diphenylmethane derivatives: Bisacodyl (e.g., Dulcolax, 10-mg tablets or 5-mg rectal suppositories) is the only currently available drug in this class, and when taken orally once daily it produces a bowel movement in about 6 hours. A suppository form, however, can produce a bowel movement within 30 to 60 minutes. Bisacodyl is a prodrug and requires *in vivo* hydrolysis for its activation. To avoid activation of the drug in the stomach and consequential gastric irritation, enteric-coated tablets should be swallowed whole without chewing. The laxative effects may be accompanied with cramps and excessive fluid loss. The drug should not be used for more than 10 days, unless advised by a physician.

3. Anthraquinone laxatives: These are plant-derived drugs that have been used as laxatives since ancient times. This group includes senna (e.g., Senokot, Nature Remedy, Ex-Lax), cascara sagrada, and aloe. All of these drugs act by inducing a low-grade inflammatory state in the small and large bowel; this inflammation induces the secretion of water and electrolytes and this is accompanied by giant migrating colonic contractions. The drugs are poorly absorbed in the small intestine and require metabolic activation by colonic bacteria to form monoanthrone derivatives. The usual dose of sennosoides, derived from senna, is 8.6 to 15 mg, which produces a bowel movement in 6 to 12 hours. The chronic use of these drugs may results in laxative dependence and a "cathartic colon" manifested by dilatation of the colon, a relative absence of myenteric plexus neurons, atrophy of the muscularis propria, and the inability to evacuate without their use. This condition is observed typically in women following chronic use of these drugs. Given this colonic pathology, anthraquinone laxatives cannot be recommended for chronic use. In fact, the official labeling for this pharmacological class mandates that these products should not be used for more than 1 week, unless directed by a physician.

4. Castor oil: Castor oil (Neoloid, Purge) is derived from the castor bean plant and contains two noxious ingredients, an extremely toxic protein, ricin, and an oil composed of the triglycerides of ricinoleic acid. In the upper intestine, the triglycerides are hydrolyzed by the pancreatic lipase enzyme to liberate ricinoleic acid, which acts in the small intestine to stimulate fluid and electrolyte secretion and thereby reduce intestinal transit time. Catharsis is produced within 1 to 3 hours. However, due to its unpleasant taste and the potential for toxicity toward the intestinal epithelium and myenteric neurons, similar to the senna, castor oil is now seldom used.

## ANTIEMETIC DRUGS

Dimenhydrinate (Dramamine, 50 mg/dose) and meclizine hydrochloride (Bonine, 25 mg/dose) are centrally acting histamine-1 (H1) receptor antagonists that are effective for the "prevention and treatment of nausea, vomiting, or dizziness associated with motion sickness." Although their mechanism of action is not well understood, it is believed that these drugs act by blocking muscarinic receptors in the brain rather than by the blockade of central histamine receptors. These drugs

possess central nervous depressant activity and consumers should be warned not to take these drugs when driving motor vehicles or operating machinery, or when taking sedatives, tranquilizers, or alcohol.

Emetrol, a phosphorylated carbohydrate solution, is an oral preparation formulated for the "relief of nausea associated with upset stomach." Each 5-ml of solution contains 1.87 g of glucose, 1.87 g of fructose, and 21.5 mg of phosphoric acid. The mechanism of the beneficial action is not fully understood, although the official labeling states that this product "has a local action on the hyperactive GI tract." The product should not be diluted. The adult dosage is 15 to 30 ml to be taken every 15 minutes until distress subsides. However, not more than five doses should be taken per hour without consulting a physician.

Of interest is the observation that bismuth subsalicylate (Pepto-Bismol) is also indicated for the treatment of "upset stomach and nausea."

## GASTROINTESTINAL DIETARY SUPPLEMENTS

Dietary supplements, which are available on an OTC basis, are frequently used for GI disorders. Unlike drugs, for which there are requirements addressing the proof of safety, efficacy, and good manufacturing practices (GMPs) to assure quality and standardization, dietary supplements do not have these legal requirements. Dietary supplements are therefore marketed on the basis of the 1994 Dietary Supplement Health and Educational Act (DSHEA) passed by the United States Congress. The DSHEA requires that the label state that the product "must not be intended to diagnose, treat, cure, or prevent any disease." Furthermore, dietary supplements do not need premarket approval or review by the FDA, as is the case for drugs, and hence their use by consumers is not based on solid scientific evidence. However, a premarket safety notification by the manufacturers is required for new ingredients. The sponsor can only claim the role of the nutrient or the dietary ingredient "intended to affect structure and function in humans."

Several digestive products and probiotics are available OTC; however, these products have not been evaluated for their clinical efficacy in controlled, double-blind studies. Digestive products are substances that promote the process of digestion in conditions characterized by lack of one or more of the specific substances that digest food. Two digestive (lactase enzyme and α-galactosidase) and one probiotic (*Lactobacillus reuteri*) products are commercially available.

### Lactase Enzymes

Lactaid and other similar preparations represent a family of products that contain a lactase enzyme derived from *Aspergillus oryzae*. Lactase aids in the digestion of lactose present in dairy products and converts it to the simple sugars, glucose and galactose. Many adults, particularly those from specific ethnic groups, such as African-Americans or Asian-Americans, have low levels of intestinal lactase. If lactose is not fully digested, it can be fermented by colonic bacteria to induce gas, bloating, cramps, and diarrhea. In such patients, ingestion of lactase may be desirable. Caplets or chewable tablets of Lactaid must be taken with the first bite of dairy food and the dosage needs to be adjusted depending on the desired response. The labeling instructs the user to seek medical attention should he/she experience any unusual symptoms, or symptoms seemingly unrelated to the condition for which the product was taken. As a dietary supplement, lactase enzyme is also added to milk to yield finished products for use by individuals who have lactose intolerance.

### α-Galactosidase

The product Beano contains the enzyme α-galactosidase, which is derived from *Aspergillus niger* and aids in the digestion of the sugars raffinose, stachyose, and/or verbascose. These sugars are present in almost all legumes (e.g., beans, peas, chickpeas, lentils, oats) and all or most of the cruciferous vegetables (e.g., cabbage, broccoli). Adverse reactions listed on the label of Beano include cramping and diarrhea as well as allergic-type reactions.

### *Lactobacillus reuteri*

The product Probiotica is a digestive product containing the bacteria *Lactobacillus reuteri*. The product label indicates that this dietary supplement provides "friendly bacteria" to the digestive system. However, there is no specific information on the label to indicate how this product provides improved digestive health. In fact, the mechanisms of action of probiotic bacteria in a variety of intestinal disorders, while supported by anecdotal clinical reports, remain the subject of investigation.

## SUMMARY AND CONCLUSIONS

The availability of drugs on an over-the-counter basis provides patients with improved access to effective therapies. However, optimal therapy with OTC drugs

requires that consumers correctly diagnose the underlying condition and safely use a desirable drug.

The OTC gastrointestinal drugs comprise six broad therapeutic categories consisting of antacids and gastric antisecretory agents, antiflatulents, antidiarrheals, laxatives, antiemetics, and dietary supplements. Antacids and histamine (H2) receptor antagonists are effective for the resolution of mild symptoms of occasional heartburn. However, H2 antagonists have a longer duration of action than do antacids when used for the self-treatment of heartburn. The product bismuth subsalicylate, which is not an antacid, is also indicated for the treatment of heartburn. Simethicone is the only approved antiflatulent drug used for the relief of painful bloating, commonly referred to as gas, in the digestive tract. The antidiarrheal drugs loperamide and bismuth subsalicylate are effective for the resolution of diarrheal symptoms. However, adsorbent antidiarrheal drugs are of no value for the treatment and prevention of acute infectious diarrhea. Laxatives of various pharmacological classes are effective for the treatment of constipation. The bulk laxatives have the most physiologic action on the colon, whereas stimulant laxatives have potential for inducing intestinal toxicity and their use should be restricted to short time periods. The histamine (H1) receptor antagonists dimenhydrinate and meclizine are effective antiemetics for the prevention and treatment of nausea and vomiting associated with motion sickness. Since 1994, diverse dietary supplements have become available and consist of either digestive enzymes (e.g., lactase, α-galactosidase) or probiotics.

Clearly, as drug patents expire for prescription-based drugs, many such drugs will likely be switched to an OTC status, thus benefiting consumers and reducing the burden of health care costs. However, it is essential that continuous vigilance is maintained to verify that consumers are safely using OTC drugs and dietary supplements.

## See Also the Following Articles

**Antacids • Anti-Diarrheal Drugs • H2-Receptor Antagonists • Laxatives • Pharmacology, Overview**

## Further Reading


Anonymous. (2002). "Physicians' Desk Reference for Nonprescription Drugs and Dietary Supplements," 23rd Ed. Thomson Medical Economics, Montvale, New Jersey.

Brass, E. P. (2001). Changing of the status of drugs from prescription to over-the-counter availability. *N. Engl. J. Med.* **345**, 810–816.

Dajani, E. Z. (2001). Gastroesophageal reflux disease: Pathophysiology and pharmacology overview. *J. Assoc. Acad. Minor. Phys.* **11**, 7–11.

Dajani, E. Z., Bianchi, R. G., East, P. F., Bloss, J. L., Adelstein, G. W., and Yen, C. H. (1977). The pharmacology of SC-27166: A novel antidiarrheal agent. *J. Pharmacol. Exp. Therap.* **203**, 512–526.

Engel, L. W., and Straus, S. E. (2002). Development of therapeutics: Opportunities within complementary and alternative medicine. *Nat. Rev. Drug Discov.* **1**, 229–236.

Hoogerwerf, W. A., and Pasricha, P. J. (2001). Agents for control of gastric acidity and treatment of peptic ulcers and gastroesophageal reflux disease. *In* "Goodman and Gilman's The Pharmacological Basis of Therapeutics" (J. G. Hardman, L. E. Limbird, and A. G. Gilman, eds.), 10th Ed., pp. 1005–1020. McGraw-Hill, New York.

Jafri, S., and Pasricha, P. J. (2001). Agents for diarrhea, constipation, and inflammatory bowel disease; agents used for biliary and pancreatic disease. *In* "Goodman and Gilman's The Pharmacological Basis of Therapeutics" (J. G. Hardman, L. E. Limbird, and A. G. Gilman, eds.), 10th Ed., pp. 1037–1058. McGraw-Hill, New York.

Krishnan, H. S., and Schaefer, M. (2000). Evaluation of the impact of pharmacist's advice giving on the outcomes of self-medication in patients suffering from dyspepsia. *Pharm. World Sci.* **22**, 102–108.

Mackerer, C. R., Clay, G. A., and Dajani, E. Z. (1976). Loperamide binding to opiate receptor sites of brain and myenteric plexus. *J. Pharmacol. Exp. Therap.* **199**, 131–140.

Shaw, M. J., Fendrick, A. M., Kane, R. L., Adlis, S. A., and Talley, N. J. (2001). Self-reported effectiveness and physicians consultation rate in users of over-the-counter histamine-2 receptor antagonists. *Am. J. Gastroenterol.* **96**, 673–676.

Sheen, C. L., and Colin-Jones, D. G. (2001). Over-the-counter drugs and the gastrointestinal tract. *Aliment. Pharmacol. Ther.* **15**, 1263–1270.

Sirgo, M. A., and Schachtel, B. P. (1997). Development of gastrointestinal drugs for over-the-counter indications. *In* "Gastrointestinal Pharmacology and Therapeutics" (G. Friedman, E. D. Jacobson, and R. W. McCallum, eds.), pp. 723–741. Lippincott-Raven Publ., Philadelphia.

Zimmerman, D. R. (1983). "The Essential Guide to Nonprescription Drugs," Harper & Row, New York.

# Pancreas, Anatomy

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**ampulla of Vater** A common channel receiving the contents of the main pancreatic duct and the common bile duct.
**common bile duct** Vessel that receives the drainage of the cystic duct of the gallbladder and common hepatic duct of the liver; it drains into the ampulla of Vater.
**duct of Santorini** A small accessory pancreatic duct located cephalad to the main pancreatic duct.
**duct of Wirsung** The main pancreatic duct.
**pancreatic islet–acinar portal system** An arterial supply network that connects the islet cells with the exocrine cells.
**sphincter of Oddi** Smooth muscle surrounding the major duodenal papilla, where the ampulla of Vater releases its contents into the descending portion of the duodenum.
**uncinate process** That portion of the pancreas that lies between the descending aorta posteriorly and the superior mesenteric artery anteriorly.

**The pancreas is a mixed endocrine and exocrine gland that crosses the midline at the transpyloric plane (L1), extending between vertebral level T10 on the left and L2 on the right. In humans, the pancreas weighs approximately 85 ± 15 g in the adult female, 90 ± 16 g in the adult male, and approximately 5 g in the newborn. Located just posterior to the stomach, the pancreas is mainly a retroperitoneal organ and not readily palpated. Imaging techniques can demonstrate pancreatic anatomy and pathology. Computed tomography (CT) and ultrasound detect inconsistencies in the pancreatic texture or masses (as observed with inflammation or tumors) and define its relationships to neighboring structures. CT, magnetic resonance imaging, and intravenous dyes that can be visualized by X-ray are used to define blood flow and vascular abnormalities. Endoscopic retrograde cholangiopancreatography is a combined endoscopic and X-ray technique in which dye is injected into the pancreatic and/or bile ducts.**

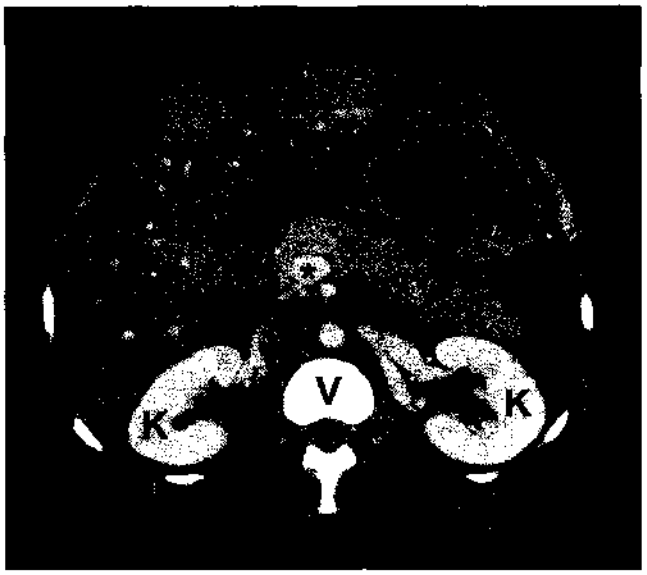


**FIGURE 1** CT scan. This axial view reveals relationships of the pancreas (P) to neighboring major structures: liver (right lobe, RL, and left lobe, LL), stomach (St), kidneys (K), vertebral body of lumbar vertebra (V), portal confluence (*), and inferior vena cava (arrow). The body of the pancreas crosses the midline and the tail of the pancreas lies in close proximity to the spleen (not seen) on the left. The distal part of the body and the tail of the pancreas are anterior to the left kidney. The body of the pancreas is anterior to the inferior vena cava and the vertebral body. Note that the pancreas is posterior to the stomach and left lobe of the liver. The portal confluence, visible in the head of the pancreas, is in close approximation to the right lobe of the liver.

## ANATOMICAL RELATIONSHIPS

In cross section, the pancreas forms an anterior convex curve, with the central portion of the pancreas located on the midline ridge formed by the upper lumbar vertebrae (Fig. 1). Abdominal trauma can lead to fracture of the pancreatic duct at two sites: where the pancreas crosses the lumbar vertebrae (the most common site) and in the pancreatic tail, where it is attached to the splenic hilum by the splenorenal ligament.

The pancreas is related to the duodenum (Fig. 2). The head and uncinate process of the pancreas rest against the duodenal bulb and descending duodenum. Rarely, ulcers may penetrate the duodenal wall and cause pancreatitis. Pancreatic tumors, inflammation, or fibrosis may cause obstruction of the duodenum. The anterior surfaces of the pancreas and duodenum are covered with peritoneum, with the exception of

 

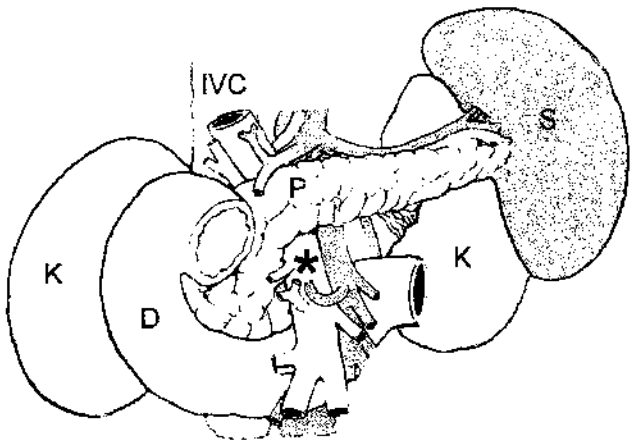


FIGURE 2 *In situ* view of the pancreas. The body of the pancreas (P) crosses the midline of the abdomen anterior to the superior mesenteric vein (*) and artery. The head of the pancreas is in the bulb of the duodenum (D) and its tail is on the left, in the splenorenal ligament that extends between the spleen (S) and the kidney (K). The inferior vena cava (IVC) is the most posterior structure.

the area at the midline where the transverse mesoderm originates.

Structures anterior to the pancreas include the stomach, omental bursa, and transverse colon. The omental bursa (lesser peritoneal sac) lies between the peritoneal coverings of the stomach (anterior) and the pancreas (posterior). The transverse colon crosses anterior to the descending duodenum and the head of the pancreas. The transverse mesocolon is formed by the peritoneal reflections off the posterior abdominal wall and anterior surfaces of the duodenum and pancreas. Pancreatic inflammation may extend into the colon and result in obstruction or bleeding. Gas in the overlying colon or small intestine may obscure visualization of the pancreas by ultrasonography.

Many structures lie posterior to the pancreas (Fig. 2). The tail and distal part of the body of the pancreas are anterior and to the right of the left kidney, with the tail encased in the splenorenal ligament. The splenic vein passes through, or is adjacent to, the pancreas. Chronic pancreatic inflammation can lead to splenic vein thrombosis, causing engorgement of the splenic vessels that connect to the stomach through the left gastric vessels. Enlargement of veins connected to the left gastric vein can result in gastric varices, which are prone to spontaneous rupture and life-threatening bleeding. The superior and inferior mesenteric vessels pass adjacent to the pancreas. If they are involved in pancreatic cancer, resection of the tumor is precluded. The portal vein originates at the junction of the splenic vein and the superior mesenteric veins. In some cases, it originates at a junction composed of three veins: the splenic vein, the superior mesenteric vein, and the inferior mesenteric vein. In either case, the portal vein drains directly into the liver. The common bile duct passes through the head of the pancreas and usually joins the main pancreatic duct to form a common channel that empties into the duodenum. Tumors, inflammation, or fibrosis within the head of the pancreas can obstruct the intrapancreatic portion of the common bile duct. This can cause jaundice and secondary biliary cirrhosis. Since the pancreas does not have a capsule, and there is no peritoneum between the dorsal part of the pancreas and structures posterior to it, tumor cells can spread to all of the structures located posterior to the pancreas.

## REGIONS OF THE PANCREAS

The pancreas has four parts: the head, neck, body, and tail. The head of the pancreas is located in the cap of the duodenum. The uncinate process is an extension of the pancreatic head that is located between the superior mesenteric artery and the abdominal part of the descending aorta. Constriction of these vessels compresses the uncinate process. The neck lies anterior to the origin of the portal vein. The body crosses the midline and lies anterior to the aorta, the splenic vein, the left suprarenal gland, the left renal vessels, the left kidney, and the left crus of the diaphragm. The tail is the only intraperitoneal part of the pancreas and lies within the splenorenal ligament.

## PANCREATIC DEVELOPMENT AND THE DUCT SYSTEM

The structure of the adult pancreatic duct system is directly related to the dual embryonic origin of the pancreas. The dorsal bud is larger than the ventral bud and gives rise to the major portion of the pancreas. It supplies all of the tail and the body and some of the head and the uncinate process. Initially, the ventral bud is a paired structure, with the left portion atrophying and the right portion continuing to grow. After rotation of the duodenum and the pancreatic buds, fusion of the dorsal and ventral ducts occurs at approximately 6 weeks of human gestation. The main pancreatic duct, called the duct of Wirsung, is surrounded by its own smooth muscle sphincter and arises from the ventral bud. It generally becomes the main conduit in the pancreas. It supplies parts of the head and the uncinate process. Approximately 80% of the time, the main pancreatic duct fuses with the common bile duct, which also

has a smooth muscle sphincter, forming a common channel called the ampulla of Vater. The ampulla of Vater releases its contents into the descending portion of the duodenum at the major duodenal papilla, which is surrounded and innervated by the smooth muscle of the sphincter of Oddi (Fig. 3). Most pancreatic duct contents are released into the duodenum at the major duodenal papilla. In addition to the main pancreatic duct, there is a small accessory duct, the duct of Santorini, which is located cephalad. In the majority of cases, it connects to the main pancreatic duct, but in a small percentage of cases, it has a separate opening into the minor duodenal papilla. The small minor duodenal papilla is cephalad to the major duodenal papilla (Fig. 3).

The pancreatic duct diameter becomes smaller from the head to the tail. Increases in the diameter of the main pancreatic duct are observed with some pathologic processes, such as obstruction by tumors or in chronic pancreatitis. However, the diameter of the pancreas may also increase with age.

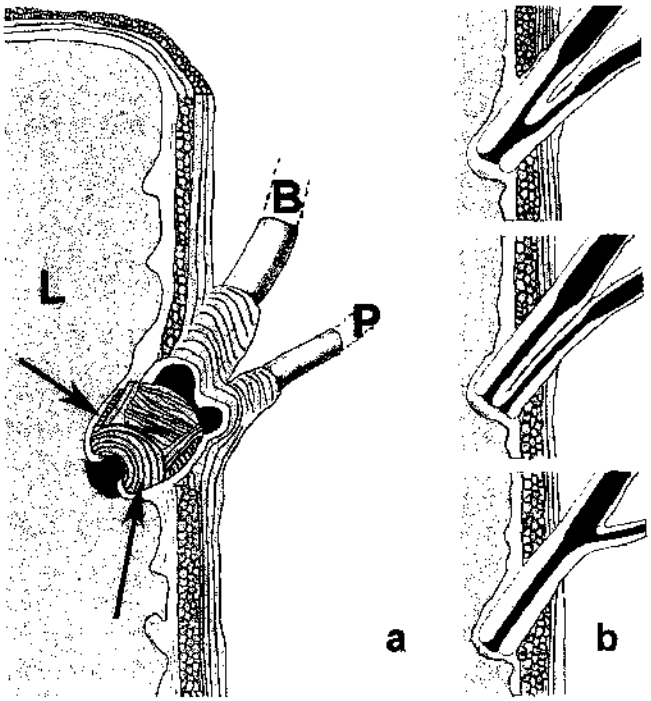


FIGURE 3 Pancreatic duct system. (a) The common bile duct (B) and the main pancreatic duct (P) join to form a common duct (ampulla of Vater). The ampulla of Vater empties its contents into the lumen (L) of the descending portion of the duodenum at the major duodenal papilla, which is surrounded by the sphincter of Oddi (arrows). Note that the main pancreatic duct and the common bile duct are surrounded by their own sphincters. (b) Three variations of the common bile duct and main pancreatic duct system. (Top) Short common channel of the two ducts. (Middle) Two separate ducts. (Bottom) Long common channel of the two ducts. Adapted from Gerard Pucher (1991). *In* "Pancreatitis (Morgenroth and Kozuschek, eds.), Walter de Gruyter.

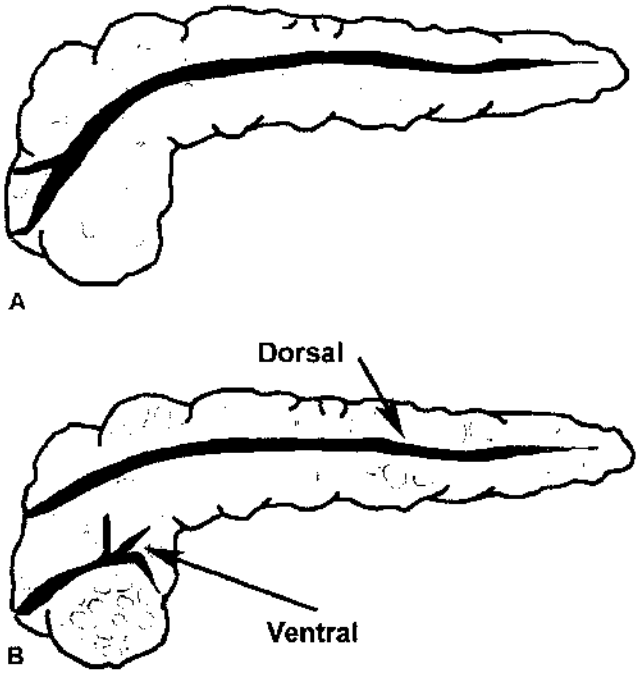


FIGURE 4 Comparison between normal pancreatic duct structure (A) and pancreas divisum (B). Note that in pancreas divisum, there are separate dorsal and ventral pancreatic ducts. There are several variations on this duct pattern.

Variations in the scheme of the pancreatic ducts are frequent. Most often, there is a small accessory duct. However, in approximately 10% of individuals, the dorsal and ventral pancreatic ducts do not fuse. This is called pancreas divisum. Most pancreatic secretions drain though a small minor papillae in pancreas divisum. In a small minority of patients, this may cause relative obstruction of the pancreatic duct that occasionally leads to pancreatitis (Fig. 4). Annular pancreas, a rare condition, may lead to obstruction in the duodenum. It is caused by the lack of atrophy of one of the portions of the ventral bud and the resulting emergence of a bifid ventral pancreatic bud that can surround and constrict the descending duodenum.

## VASCULATURE AND LYMPHATICS

Arterial supply to the pancreas is provided by the splenic artery, the pancreatic branches of the gastroduodenal and superior mesenteric arteries, the superior posterior pancreaticoduodenal artery (a branch of the gastroduodenal artery), and the inferior pancreaticoduodenal artery (a branch of the superior mesenteric artery). The splenic artery, a branch of the celiac trunk, lies along the upper border of the pancreas and forms

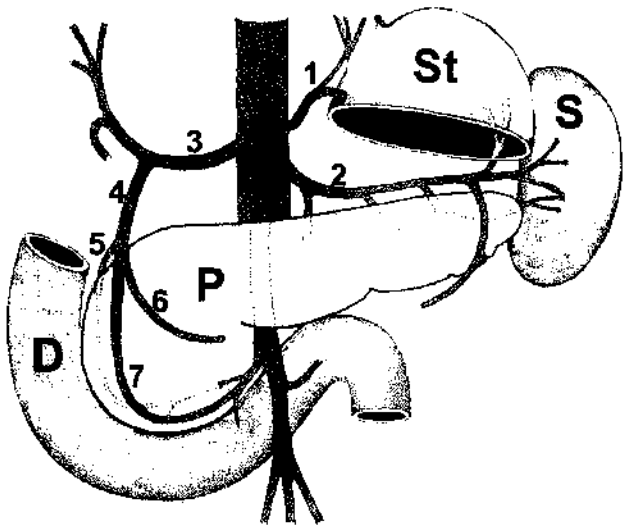


FIGURE 5 Arterial supply to the pancreas. The major arterial supply to the pancreas is from the splenic artery (2) on the superior border of the pancreas and the posterior (5) and anterior (7) superior pancreaticoduodenal arteries, which are branches of the gastroduodenal artery (4). Other vessels in the region include the left gastric (1), common hepatic (3), right gastroepiploic (6), and superior mesenteric (asterisk) arteries.

arcades with the pancreatic branches of the gastroduodenal and superior mesenteric arteries (Fig. 5). The arcades supply the body and tail of the pancreas. The intimate association of the pancreas with critical vascular structures often leads to direct involvement of pancreatic cancer with these blood vessels. This is often the reason that pancreatic cancers cannot be removed surgically. A pancreatic portal system connects the endocrine and exocrine pancreas, allowing arteries supplying the islets to flow directly to the acini located in the immediate vicinity of the islets. Venous drainage of the pancreas occurs by way of the splenic vein, which lies posterior to the pancreas. Venous blood exiting the pancreas flows directly into the liver through the portal vein.

Lymphatic drainage from the pancreas is carried to the pancreaticosplenic, pancreaticoduodenal, subpyloric, and hepatic lymph nodes. Lymph from these nodes flows through the celiac lymph nodes into the intestinal lymphatic trunk and the thoracic duct, ultimately draining into the junction of the left jugular and the left subclavian veins.

## NERVOUS INNERVATION

The autonomic nervous system (ANS) plays a major role in the sensory and motor innervations of the pancreas. Nerve fibers are unevenly distributed throughout the pancreas, with the ANS supply being richer in the head of the pancreas than in the tail. The right celiac, hepatic, and superior mesenteric nerve plexuses innervate the head and neck of the pancreas. The celiac plexus and splanchnic neurological networks supply the pancreatic body and tail.

General sensation from the pancreas is carried by visceral afferent fibers of the vagus nerve. Pancreatic visceral pain carried by sympathetic fibers is referred to dermatomes T5–T10, which mark the upper abdomen in the area of the stomach. Severe abdominal pain is a characteristic of both acute and chronic pancreatitis. With chronic disease, the pain is associated with changes in neuronal architecture and changes in neurotransmitter content. Disruption of the perineural sheath may allow toxic substances to come into direct contact with nerve fibers. In patients suffering from chronic pancreatitis, inflammatory cells (lymphocytes, granulocytes, and macrophages) are found around nerves and ganglia supplying the pancreas and the size of nerves is greatly increased. In pancreatic cancer, tumor cells disrupt the perineural sheath and invade the underlying nerve fibers. Severe back pain may be due to the activation of nerve fibers located in the posterior abdominal wall. Changes in neurotransmitter content include the release of increased amounts of two pain transmitter substances: calcitonin gene-related peptide (CGRP) and substance P.

Recent research suggests that some pancreatic pain may be the result of proteolytic activation of the protease-activated receptor PAR-2, a member of the G-protein-coupled receptor family. PAR-2 expression has been detected on a subset of peripheral peptidergic neurons and is involved in the neurogenic component of inflammation. In pancreatitis, PAR-2 may be activated by pathologically generated trypsin from acinar cells or tryptase from mast cells. Pancreatic pain can also be generated by edema, pancreatic duct distension, or ischemia.

Pancreatic secretion is controlled by the parasympathetic and sympathetic nerve fibers as well as peptidergic nerve fibers. Nerve fibers secrete neurotransmitters (acetylcholine from parasympathetic fibers, norepinephrine from sympathetic fibers, and various peptides from peptidergic fibers) along the length of their axons. The neurotransmitters diffuse to target cells, bind to cell surface receptors, and work through signal transduction pathways to stimulate or inhibit pancreatic secretion. Since sympathetic terminals are predominantly associated with blood vessels, decreased blood flow is also related to decreased secretion. Corticotropin-releasing factor (CRF) and CGRP also exert effects on pancreas secretion indirectly, through sympathetic pathways. CRF and CGRP cause the decreases in pancreatic secretion associated with stress. Vagal parasympathetic fibers are also major regulators of

interdigestive secretion, supplying pancreatic acini and islets. They stimulate secretion by releasing acetylcholine, which interacts with the M3 receptor on the acinar cell. A major component of pancreatic secretion stimulated by either cholecystokinin (CCK) or secretin is probably indirect. In response to a meal, CCK is released from I cells and secretin is released from S cells, in the duodenum. These ligands bind to neural pathways and release neurotransmitters that stimulate receptors on acinar and duct cells. They also may have direct effects on exocrine cells. Acetylcholine plays a major role in this pathway. Another major pathway regulating pancreatic secretion is mediated by serotonin, released when food is in the duodenum and interacts with 5-hydroxtryptamine receptors.

Peptidergic nerves in the pancreas exert effects on exocrine tissue but are vulnerable to proteases, so they act in a paracrine manner by releasing peptides that stimulate secretion by neighboring acinar cells. Somatostatin, enkephalin, and pancreastatin are examples of peptides that act in a paracrine manner.

In summary, the pancreas is a mixed endocrine and exocrine gland that crosses the midline at the transpyloric plane (L1) of the abdomen. It consists of four parts: the head, neck, body, and tail. Except for the tail, which is intraperitoneal, the gland is retroperitoneal. This fact, combined with the absence of a capsule, explains the various pathological conditions that arise due to the spread of pancreatic tumors to other retroperitoneal organs. The duct system, of dual embryonic origin, releases its contents into the descending portion of the duodenum. Anastomosis of several major arteries supplies the pancreas. Venous blood drains into the portal vein. Innervation to the pancreas is supplied by the vagus nerve and the ANS. Imaging techniques used to examine the pancreas include computed tomography, ultrasound, endoscopic retrograde cholangiopancreatography, and X-rays.

## See Also the Following Articles

**Automonic Innervation • Circulation, Overview• Endocrine Pancreas • Exocrine Pancreas • Gastrointestinal Tract Anatomy, Overview • Pancreatic Enzyme Secretion (Physiology)**

## Further Reading

Adler, G., Beglinger, C., Braun, U., Reinshagen, M., Koop, I., Schafmayer, A., Rovati, L., and Arnold, R. (1991). Interaction of the cholinergic system and cholecystokinin in the regulation of endogenous and exogenous stimulation of pancreatic secretion in humans. *Gastroenterology* 100, 537–543.

Buchler, M., Weihe, E., Friess, H., Malfertheiner, P., Bockman, E., Muller, S., Nohr, D., and Beger, H. G. (1992). Changes in peptidergic innervation in chronic pancreatitis. *Pancreas* 7, 183–192.

Friess, H., Shrikhande, S., Shrikhande, M., Martignoni, M., Kulli, C., Zimmermann, A., Kappeler, A., Ramesh, H., and Buchler, M. (2002). Neural alterations in surgical stage chronic pancreatitis are independent of the underlying aetiology. *Gut* 50, 682–686.

Gorelick, F. S., and Jamieson, J. D. (1994). The pancreatic acinar cell structure–function relationships. *In* "Physiology of the Gastrointestinal Tract" (L. R. Johnson, ed.), 3rd Ed., Vol. 2, pp. 1353–1376. Raven Press, New York.

Hoogerwerf, W. A., Zou, L., Shenoy, M., Sun, D., Micci, M. A., Lee-Hellmich, H., Xiao, S. Y., Winston, J. H., and Pasricha, P. J. (2001). The proteinase-activated receptor 2 is involved in nociception. *J. Neurosci.* 21, 9036–9042.

Li, Y., Wu, X. Y., Zhu, J. X., and Owyang, C. (2001). Intestinal serotonin acts as paracrine substance to mediate pancreatic secretion stimulated by luminal factors. *Am. J. Physiol. Gastrointest. Liver Physiol.* 281, G916–G923.

# Pancreas, Development

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**homeobox/homeodomain** Specific sequences of transcription factor nucleotides and amino acids that confer a DNA binding patterning/regulation capacity.

**lateral inhibition** Process by which a single, centrally located cell self-determines its differentiation and, in doing so, inhibits a similar fate selection by adjacent lateral cells.

**lineage selection** Process by which developmental fate choices are made during organogenesis between different cell lineage types.

**Pdx-1** Patterning transcription factor required for early development of the embryonic pancreas.

**protodifferentiated** Early state of differentiation wherein cells exhibit low-level expression of lineage-specific genes, but have not acquired the higher expression levels characteristic of fully differentiated cells.

**The pancreas develops through the evagination of early endoderm. Cells then remain in the epithelium to become the ductal–acinar network or migrate out of the epithelium to give rise to the endocrine cells. These processes are controlled through a complex array of intracellular and extracellular molecular influences. Defects in these pathways can lead to various pathologic states.**

## INTRODUCTION

The pancreas develops from the caudal foregut, where endodermal cells give rise to a ventral and dorsal pancreatic bud. These two buds then fuse and mesenchymal factors induce the early pancreatic epithelium to undergo a complex pattern of cellular differentiation and lineage selection to yield both epithelial exocrine (acinar and ductal) and nonepithelial endocrine cells. Studies of pancreatic organogenesis have identified several morphogenetic signals, patterning transcription factors, and pathogenetic mechanisms of pancreatic abnormalities. The following overview is a description of the present knowledge of pancreatic organogenesis and morphogenesis.

## EMBRYONIC ANATOMY

At approximately 5 weeks of gestation in the human, the pancreatic dorsal and ventral buds evaginate from the endodermal lining of the caudal foregut. The ventral bud moves with the axial rotation of the gut tube during week 6, as the C-loop of the duodenum takes its final position and comes to lie behind and below the dorsal bud. By gestational week 7, fusion of the two pancreatic buds occurs (see Fig. 1).

The most clinically relevant gross anatomy of the exocrine pancreas is the duct system. The main

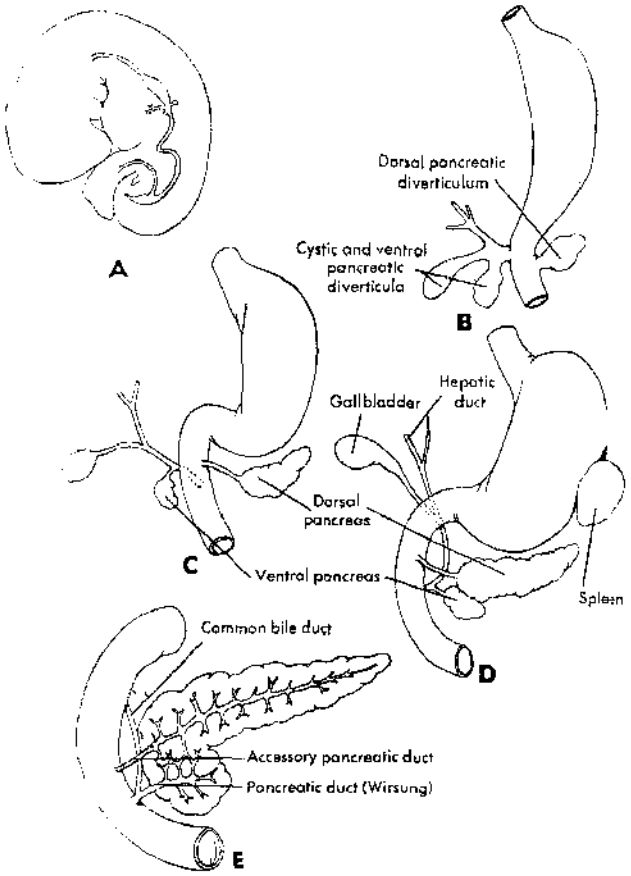


**FIGURE 1** Development of the derivatives of the human caudal foregut. (A) Orientation of the gut within a human embryo at about 30 days of gestation. (B–D) The stomach, duodenum, and pancreatic and hepatic diverticula at approximately 30, 33, and 36 days. (E) The definitive relationships of the pancreatic and common bile ducts. Reproduced with permission from Allan, F. G. (1969). "Essentials of Human Embryology." New York: Oxford University Press.

 

pancreatic duct (duct of Wirsung) is formed by fusion of the distal dorsal duct with the entire ventral duct. This main pancreatic duct drains into the duodenum via the ampulla of Vater. The proximal dorsal duct usually persists as an accessory duct, communicates with the main duct, and opens into the duodenum at the minor papilla. When present, this accessory duct is called the duct of Santorini. Approximately 10% of humans with otherwise normally developed pancreata do not have duct fusion, and the entire dorsal duct drains via the minor papilla. The ventral bud develops into the inferior head and uncinate process of the mature pancreas; the dorsal bud provides the remainder. The pancreas is highly vascular and has extensive lymphatic drainage. The connective tissue, septae, and lymphatics of the adult gland are derived from the splanchnic mesoderm.

Histologically, the pancreas is composed of two distinct tissue types, exocrine and endocrine. The exocrine pancreas consists of lobules of acinar cells at the tips of branched ducts. The acinar cells develop zymogen granules containing proenzymes for over 20 digestive enzymes. Zymogens release these proenzymes (nucleases, proteases, amylase, and lipase), into the gastrointestinal tract, where they are activated and participate in digestion. The function of the healthy exocrine pancreas is under complex regulation by hormones, including cholecystokinin (CCK), neurohormones, and secretin.

The cells of the endocrine pancreas constitute only 1–2% of the adult gland, but early in differentiation these represent a major component of the developing pancreas. Clusters of endocrine cells, the islets of Langerhans, form from cells that bud off of the exocrine ducts. Four types of endocrine cells secrete their peptide hormones into the bloodstream from the islets. The majority of pancreatic endocrine cells are beta cells, which produce insulin and amylin (an insulin antagonist). The other three cell types are glucagon-secreting alpha cells, somatostatin-producing delta cells, and the pancreatic polypeptide (PP)-secreting cells. These islets do not arise from a single progenitor cell, and the cellular content of islets is variable. For example, islets with a higher concentration of pancreatic polypeptide-producing cells are found in the head of the pancreas, which derives from the embryologic ventral bud.

## CELLULAR DIFFERENTIATION AND MORPHOGENESIS

The normal structural development of the embryonic pancreas during early gestation has been well described. Specifically, Wessells and Cohen in 1967 and Pictet and Rutter in 1972 delineated the morphogenesis of the pancreas in the rat. The first morphologic evidence of the embryonic pancreas, an evagination of the foregut dorsal and ventral endoderm, forms the dorsal and the ventral pancreatic buds, respectively. Dorsal bud evagination occurs first and requires previous contact with overlying notochord, followed by dorsal aorta. The process of evagination and subsequent further growth and differentiation of the pancreatic buds seems to require the presence of the overlying splanchnic mesoderm. This early evagination occurs at 9–10 days of gestation in the mouse.

The developing pancreatic bud starts as a simple sheet of epithelium, which then quickly becomes highly folded. Progressive growth and branching lead to the exocrine (ducts and acini) network. This ductal–acinar structure of the pancreas is evident by 14.5 days in the mouse. Detected throughout the early development of the pancreas, endocrine cells appear to break away and form nonepithelial clusters of endocrine cells that will become vascularized and form the islets of Langerhans.

Pancreas-specific cytodifferentiation has been described by Pictet and Rutter as beginning with a "protodifferentiated" epithelial cell. Exocrine and endocrine cell lineages both originate from these morphologically undifferentiated cells. Expression of lineage-specific mRNA, such as insulin and amylase RNA in these cells, suggests an early commitment to a lineage. Insulin and glucagon genes are expressed prior to dorsal pancreatic bud evagination at embryonic day 9.5 in the mouse. Amylase and other acinar enzyme genes are first expressed around days 11–12 in the mouse.

## MOLECULAR INFLUENCES

Although the morphologic and functional development of the pancreas has been well described, the details of the molecular influences regulating pancreatic cell proliferation and differentiation remain elusive. As mentioned previously, contact of early endoderm with the notochord is necessary to induce evagination and subsequent pancreatic differentiation. This interaction is mediated through notochord production of fibroblast growth factor-2 (FGF-2) and activin B, which inhibit the production of sonic hedgehog (SHH) by the endodermal cells that form the pancreas. This SHH suppression is specific to the prepancreatic area. This backdrop of extracellular signaling, accompanied by expression of patterning transcription factors (Pdx-1 and Hlbx9), leads to the early development of the embryonic pancreas. Differentiation pathways determined by homeodomain proteins such as Pdx-1 and Hlbx9 are further modulated by the expression of secondary patterning genes. For example, neurogenin 3, a helix–loop–helix

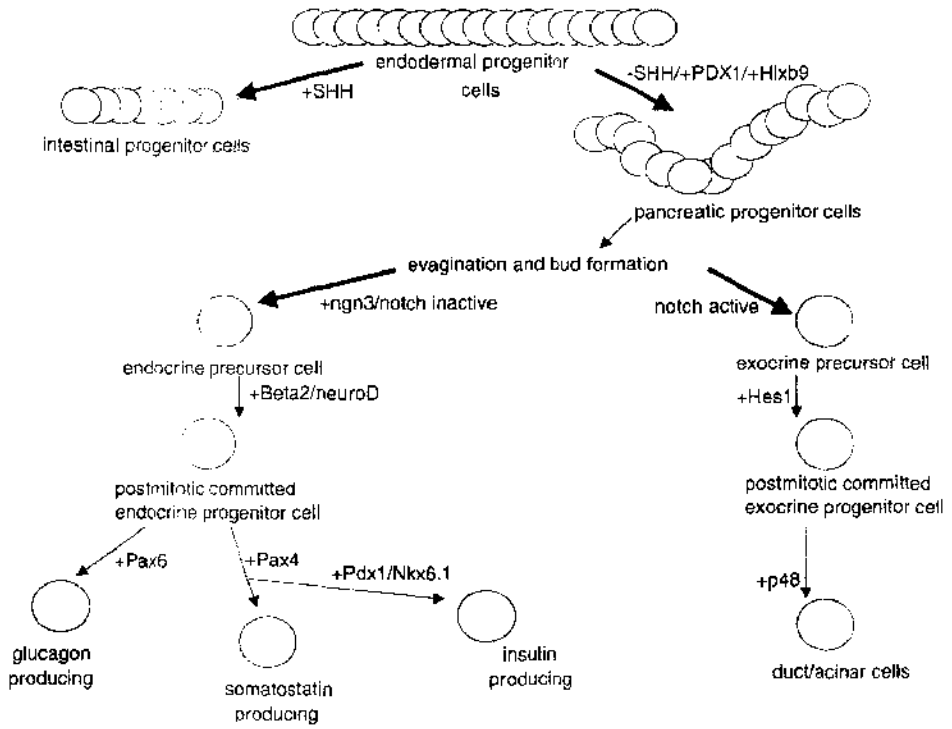


FIGURE 2 Molecular influences and cell lineage map for differentiation of the pancreas. SHH, Sonic hedgehog; ngn3, neurogenin 3.

(HLH) protein, has been found to be necessary for the commitment of Pdx-1-positive cells to become pancreatic endocrine cells. Notch signaling, through mechanisms similar to pathways of neurogenesis called "lateral inhibition," opposes neurogenin 3 signaling and leads to exocrine differentiation. Further levels of lineage selection occur after these events (see Fig. 2).

In endocrine differentiation, Pax4 and Pax6 confer specific differentiation of the glucagon cell (alpha cell) and the insulin cell (beta cell), respectively. In exocrine differentiation, p48 is an HLH protein that is necessary for exocrine differentiation and activates acinar genes. Much of this secondary differentiation beyond the initial pancreatic commitment is mediated by factors in the surrounding pancreatic mesenchyme. FGFs and laminins are examples of such critical mesenchyme-derived factors.

## DEVELOPMENTAL ABNORMALITIES

A rare embryologic abnormality of the pancreas is complete agenesis; this has been associated with mutation of the Pdx-1 gene and is frequently fatal in the newborn. A heterozygous Pdx-1 mutation leads to one form of mature-onset diabetes of the young (MODY). Partial pancreatic agenesis describes the otherwise normal pancreas with a portion absent, typically the dorsal pancreas. Hypoplasia of the pancreas, or "lipomatous pseudohypertrophy of the pancreas," is the congenital absence of secondary exocrine structure development. The pancreas has normal islets, but the ductal structures have been replaced by fat.

Pancreas divisum is noncommunication of the ducts in the dorsal and ventral pancreas. Failure of fusion between the main duct (ventral) and the accessory duct (dorsal) results in most of the pancreas draining through the minor papilla via the persistent duct of Santorini. Pancreas divisum is the most common anomaly of the pancreas (~5–10%), and may be more prominent in patients with pancreatitis (16–25%).

Failure of proper pancreatic rotation is thought to lead to a complete ring of pancreatic tissue around the second portion of the duodenum (annular pancreas). Annular pancreas is frequently associated with other anomalies, such as trisomy 21 and duodenal atresia.

Persistent hyperinsulinemic hypoglycemia of infancy (PHHI), also termed nesidioblastosis, is a condition wherein the insulin cells have faulty glucose sensing and thus overproliferate and overproduce insulin. PHHI is often due to mutations in the sulfonylurea receptor 1 (SUR1) () or Kir6.2, and is sometimes associated with the Beckwith–Wiedemann syndrome and multiple endocrine neoplasia type 1(MEN 1). Duct–endocrine proliferation, with new

islet formation from the pancreatic duct epithelium, characterizes nesidioblastosis, but these findings can be seen in the normal neonate as well. Frequently a difficult clinical and pathologic diagnosis, nesidioblastosis requires prompt medical and surgical treatment to avoid brain damage from severe hypoglycemia.

## See Also the Following Articles

**Development, Overview • Endocrine Pancreas • Exocrine Pancreas • Pancreas, Anatomy**

## Further Reading


Allan, F. G. (1969). "Essentials of Human Embryology." Oxford University Press, New York.

Edlund, H. (2001). Developmental biology of the pancreas. *Diabetes* 50(Suppl. 1), S5–S9.

Gittes, G. K., and Rutter, W. J. (1992). Onset of cell-specific gene expression in the developing mouse pancreas. *Proc. Natl. Acad. Sci. U.S.A.* 89, 1128–1132.

Hill, D. J., and Duvillie, B. (2000). Pancreatic development and adult diabetes. *Pediatr. Res.* 48, 269–274.

Maldonado, T. S., Crisera, C. A., Kadison, A. S., Longaker, M. T., and Gittes, G. K. (2000). Role of mesenchymal–epithelial interactions in pancreas development. *In* "Molecular Basis of Pancreatic Endocrine Development and Function" (M. Hussain, C. Miller, and J. Habener, eds.), pp. 170–188. Kluwer Academic Publ., Boston.

Peters, J., Jürgensen, A., and Klöeppel, G. (2000). Ontogeny, differentiation and growth of the endocrine pancreas. *Virchows Arch.* 436, 527–538.

Pictet, R., and Rutter, W. J. (1972). Development of the embryonic endocrine pancreas. *In* "Handbook of Physiology" (D. F. Steiner and N. Frenkel, eds.), Sect. 7, Vol. 1. American Physiological Society, Williams & Wilkins, Philadelphia, PA.

Polak, M., Bouchareb-Banaei, L., and Scharfmann, C. P. (2000). Early pattern of differentiation in the human pancreas. *Diabetes* 49, 225–232.

Schwitzgebel, V. M., Scheel, D. W., Connors, J. R., Kalamaras, L. J. E., Anderson, D. J., Sussel, L., Johnson, J. D., and German, M. S. (2000). Expression of neurogenin3 reveals an islet cell precursor population in the pancreas. *Development* 127, 3533–3542.

Slack, J. M. W., (1995). Developmental biology of the pancreas. *Development* 121, 1569–1580.


# Pancreas, Nutritional Effects on


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**kwashiorkor** Protein deficiency state with adequate caloric intake.

**marasmus** Deficiency state resulting from deprivation of both proteins and calories.

**nutritional pancreatitis** Form of nonalcoholic chronic pancreatitis prevalent in India and other tropical countries.

**Inadequate nutrition, especially of protein, may lead to pancreatic atrophy or in some cases chronic pancreatitis or diabetes. Both the exocrine and endocrine components of the pancreas can be injured. Factors causing injury to the pancreas directly or indirectly interfere with both components to a varying degree, although pancreatic exocrine and endocrine components have considerable functional reserve and malabsorption is not seen until 90% of the pancreas is lost.**

## MALNUTRITION AND EXOCRINE PANCREATIC INJURY

### Protein Deficiency

Among the specialized organs of the body, the pancreas (along with liver and small intestine) has the highest rate of protein synthesis. The acinar cells synthesize and secrete between 6 and 20 g of digestive enzymes in 24 hours. Consequently, the pancreas is extremely vulnerable to short- or long-term protein deficiency. Protein energy malnutrition (PEM) is the most important public health problem in developing countries. Malnutrition in affluent nations is often occult, resulting from chronic alcoholism, drug abuse, immunodeficiency states, and problems associated with old age.

Severe nutritional deficiency causes initially reversible and finally irreversible changes. In an experimental study on Bonnet monkeys, animals on protein-deficient, normal carbohydrate diets showed atrophy of pancreatic tissue with replacement with adipose tissue. Animals on low-protein, high-carbohydrate diets showed severe changes. The additional carbohydrate seemed to harm the pancreas more than normal carbohydrate consumption. The low-protein, high-carbohydrate diet mimics the usual diet of the population groups in most developing nations. Other experimental studies have shown recovery of pancreatic function when protein deficiency is corrected, depending on the severity and duration of malnutrition. Clinical observations support experimental studies. Children dying of kwashiorkor have small fibrosed pancreases along with atrophic intestinal mucosa. In children suffering from marasmus and kwashiorkor, pancreatic enzyme output is decreased with no change in $HCO_3^-$ output. The pancreatic ductules, which produce $HCO_3^-$, are usually well preserved in kwashiorkor.

## Micronutrient Deficiencies

Clinical malnutrition is seldom a pure protein deficiency state. Multiple deficiencies of trace elements and vitamins occur. Unopposed free radicals (FRs) are potential mediators of injury to many organs, including the pancreas. The roles played by antioxidant enzymes, which include a mineral in their structure (metalloenzymes), and antioxidant vitamins (such as vitamins A, E, C, and β-carotene) are increasingly clear. Zinc, an essential micronutrient, is a component of enzymes such as DNA polymerase, RNA polymerase, and reverse transcriptase, which are involved in protein synthesis. Experimental studies have shown that zinc deficiency promotes acinar cell degeneration. Clinical zinc deficiency occurs in chronic alcoholism, cirrhosis of the liver, sickle cell disease, and other conditions. Similarly, selenium is an important trace element because it is a component of the enzyme glutathione peroxidase. A selenium-deficient diet in chicks causes pancreatic atrophy. Clinical selenium deficiency occurs in chronic alcoholics and cigarette smokers.

There is no pancreatic disease that can be solely attributed to malnutrition. However, a form of nonalcoholic chronic pancreatitis, prevalent in India and other tropical countries, known as tropical or nutritional pancreatitis, is reported to occur in children and young adults of low-income groups. Although the etiology for tropical pancreatitis is not yet elucidated, experimental data coupled with epidemiological observations have indicated that malnutrition might play a major role in its pathogenesis.

## Malnutrition and Endocrine Pancreatic Injury

The role of malnutrition as a cause for endocrine pancreatic injury has only recently been recognized. Although diabetes is often recognized to be a complication of being overweight, abnormal glucose tolerance is a feature of malnutrition. A reduction in insulin secretory capacity is noted in malnourished animals in experimental studies. The functional damage to B cells in malnutrition initially starts as high levels of insulin (hyperinsulinemia) in early stages of subclinical malnutrition and progresses to low levels of insulin (hypoinsulinemia) with the onset of frank malnutrition. In kwashiorkor, there is islet cell hypertrophy in early stages, followed by atrophy. Malnutrition-related diabetes mellitus is recognized to be a subtype of diabetes. It is not clear whether protein deficiency is the sole cause of this diabetes.

## See Also the Following Articles

**Dietary Reference Intakes (DRI): Concepts and Implementation • Malnutrition • Pancreatitis, Chronic • Protein-Calorie Deficiency—"Kwashiorkor"**

## Further Reading

Pitchumoni, C. S., and Scheele, G. (1993). Interdependence of nutrition and exocrine pancreatic function. *In* "The Pancreas Biology: Pathobiology and Disease" (Go, *et al.*, eds.). Raven Press, New York.

Rao, H. R. (1988). Diabetes in the undernourished: Coincidence or consequence. *Endocr. Rev.* 9, 67–87.

Sandhyamani, S., Vijayakumari, A., and Nair, B. (1999). Bonnet monkey model for pancreatic changes in induced malnutrition. *Pancreas* 18, 84–95.

# Pancreatic Anomalies

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**endoscopic retrograde cholangiopancreatography** A procedure whereby pancreatic and biliary ducts are visualized by endoscopic injection of contrast medium.
**stenosis** An area of narrowing.

The pancreas develops during the fourth week of gestation, arising from the endodermal lining of the duodenum. From this anlage, two pancreatic pouches, dorsal and ventral, develop, which ultimately give rise to the body/tail and head/uncinate processes of the pancreas, respectively. By the sixth week of gestation, the ventral pouch assumes a position adjacent to the dorsal pouch through the process of clockwise migration as the primitive duodenum rotates to assume its characteristic C-shaped configuration. Fusion of the dorsal and ventral primordia and their ductal systems is achieved by the eighth week. At the time of birth, the pancreatic parenchyma is unified and the accessory and main pancreatic ducts are fused. Malformations of pancreatic embryology include annular pancreas, pancreas divisum, and heterotopic pancreas.

## ANNULAR PANCREAS

Annular pancreas occurs when the ventral pancreatic pouch fails to properly rotate clockwise posteriorly around the duodenum (see Fig. 1). Thus, the ventral pouch lies anterior to the duodenum in this anomaly. The duodenum can become partially or completely obstructed by the encircling pancreatic ring (Fig. 2). The band of pancreatic tissue commonly lies proximal to the major duodenal papilla. Microscopically, pancreatic tissue often is found to invade the duodenal wall into the muscularis layer. Other congenital defects associated with annular pancreas include duodenal atresia, Down's syndrome (trisomy 21), intracardiac defects, intestinal malrotation, and tracheoesophageal fistula. Annular pancreas is the most common anomaly obstructing the duodenum in infants, who may present with feeding intolerance and vomiting. On examination, visible peristalsis and distension may be appreciated due to the obstruction. Less commonly, the existence of annular pancreas may not become manifest until adulthood. Patients may complain of bloating, pain, or vomiting. Upper gastrointestinal obstruction, peptic ulceration, and pancreatitis may result from annular pancreas. Diagnosis is facilitated by plain abdominal radiograph, which classically reveals the "double-bubble" sign characteristic of gastric and duodenal dilation secondary to duodenal obstruction. Often, however, upper gastrointestinal contrast study is necessary to document obstruction. Endoscopic retrograde cholangiopancreatogram (ERCP) may also be useful in demonstrating ductal anomalies found with this condition.

Treatment is operative when obstructive symptoms develop. Bypass of the obstruction by duodenojejunostomy is preferred over resection of the annular pancreatic tissue due to the high predisposition to develop pancreatic and duodenal fistulas.

## PANCREAS DIVISUM

Failure of the ventral and dorsal pancreatic ductal systems to fuse results in pancreas divisum. In this disorder, the majority of the pancreas is drained through the accessory pancreatic duct (duct of Santorini) into the minor duodenal papilla (Fig. 3). Pancreatic secretions from the uncinate process and portions of the pancreatic head, derived from the ventral anlage, drain via the major duodenal papilla (via the duct of Wirsung), separate from the remainder of the pancreas. Pancreas divisum is relatively common, demonstrated in 5 to 10% of subjects by autopsy or by ERCP.

Manifestations of pancreas divisum occur uncommonly in childhood. Controversy exists as to whether pancreas divisum has a causative role in recurrent idiopathic acute pancreatitis, chronic pancreatitis, and chronic abdominal pain. Some investigators believe that stenosis of the minor duodenal papilla must coexist with pancreas divisum for pancreatitis to develop. Diagnosis of pancreas divisum is made by ERCP; on cannulation of the accessory papilla, the duct of Santorini is found to span the length of the pancreas without communicating with the duct of Wirsung.

Given the uncertainty of a causal relationship between pancreas divisum and pancreatitis, no specific intervention is advised for mild or single episodes of pancreatitis. Severe or recurrent bouts of pancreatitis may warrant therapeutic invention. Both endoscopic and surgical approaches have been

 

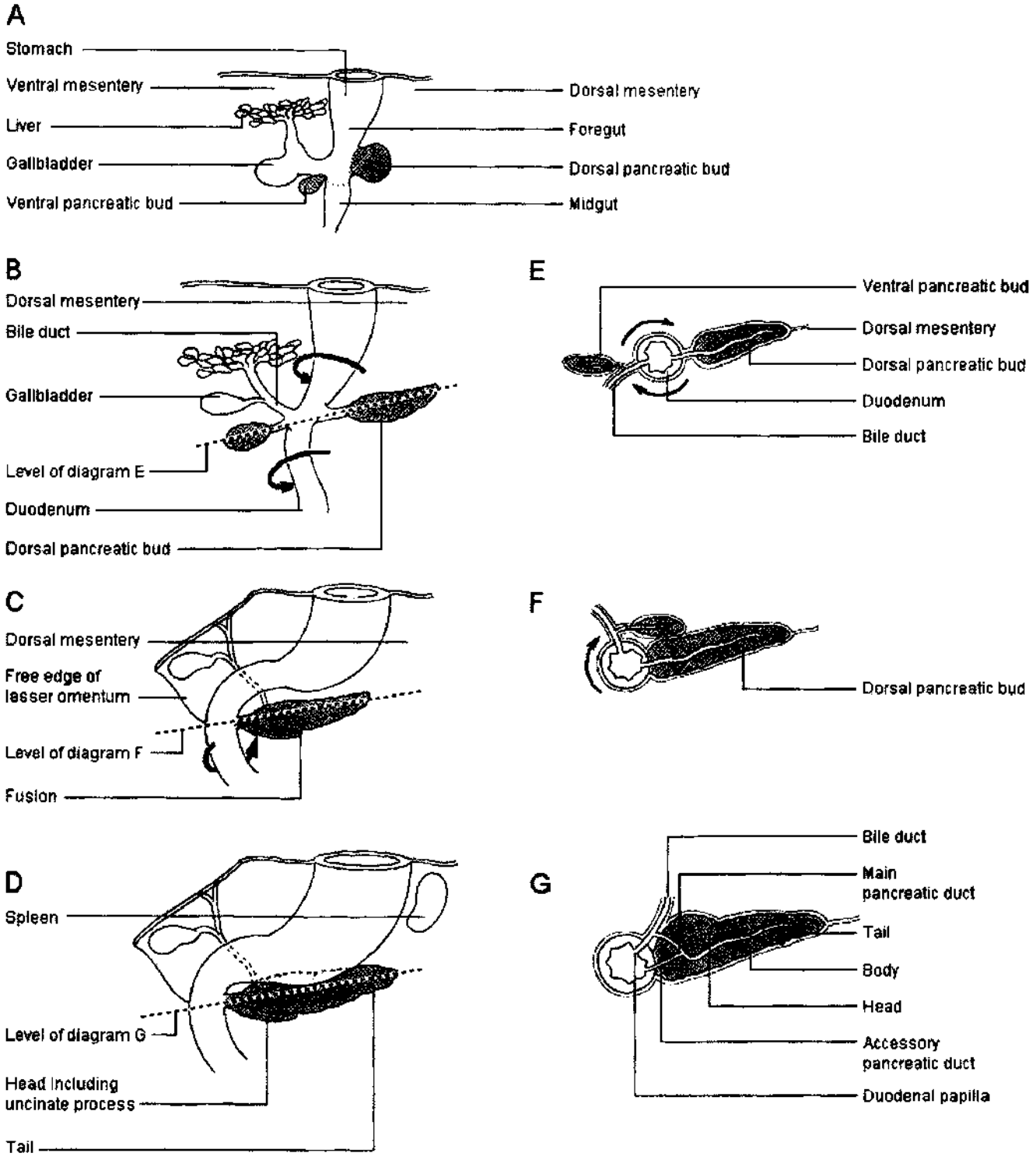


FIGURE 1 Development of the fetal pancreas from the fifth to the eighth week. Rotation (arrows) of the duodenum brings the ventral bud into apposition with the dorsal bud, with subsequent fusion. Reprinted from Anderson, D. and Brunicardi, F. *In* "Surgery: Scientific Principles and Practice" (L. Greenfield, M. Mulholland, K. Oldham, G. Zelenock, and K. Lillemoe, eds.), 2nd Ed., with permission. Copyright Lippincott-Raven Publishers, 1997.

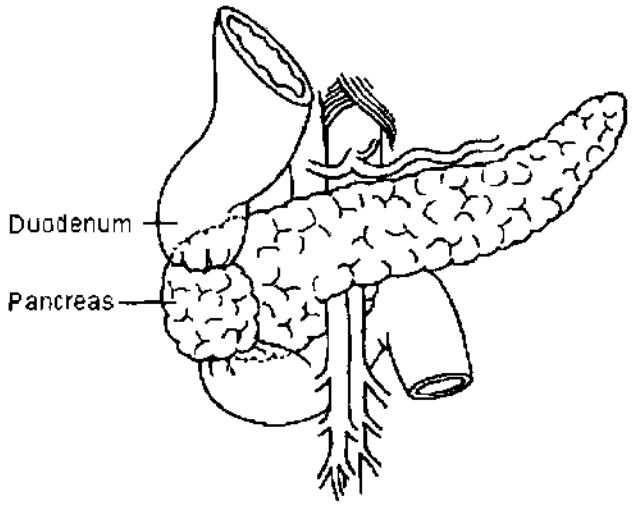


FIGURE 2 Annular pancreas with consequent duodenal obstruction secondary to the encircling pancreatic ring. Reprinted from Oldham, K. *In* "Surgery: Scientific Principles and Practice" (L. Greenfield, M. Mulholland, K. Oldham, G. Zelenock, and K. Lillemoe, eds.), 2nd Ed., with permission. Copyright Lippincott-Raven Publishers, 1997.

described. Stenosis of the minor duodenal papilla or stricture of the accessory pancreatic duct may be approached endoscopically with dilation, stent placement, or sphincterotomy. Surgical approaches include transduodenal sphincteroplasty of the minor papilla, pancreatic head resection, and pancreaticojejunostomy.

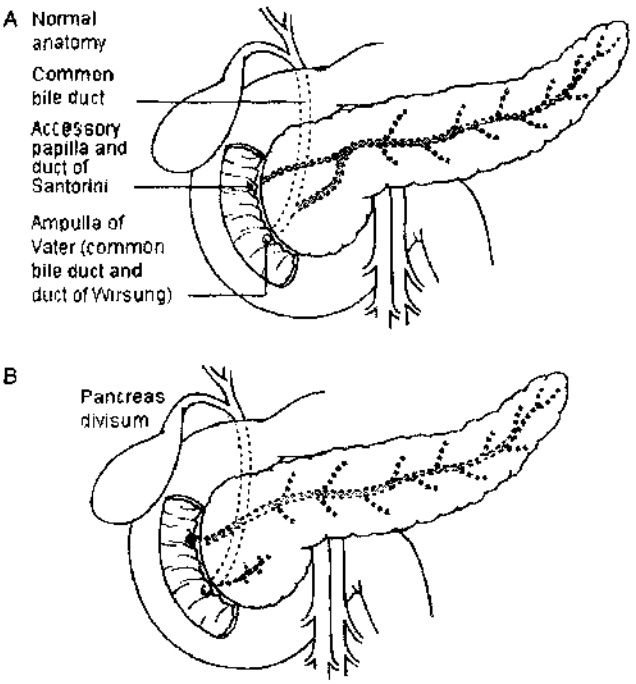


FIGURE 3 (A) Normal ductal anatomy. (B) Pancreas divisum. No communication exists between the duct of Wirsung and the duct of Santorini. Most of the pancreas is drained through the duct of Santorini. Reprinted from Coran, A. *In* "Surgery: Scientific Principles and Practice" (L. Greenfield, M. Mulholland, K. Oldham, G. Zelenock, and K. Lillemoe, eds.), 2nd Ed., with permission. Copyright Lippincott-Raven Publishers, 1997.

## HETEROTOPIC PANCREAS

When pancreatic tissue develops outside of the main pancreatic body, these aberrant rests of tissue are referred to as heterotopic pancreas. Heterotopic pancreatic tissue may be found anywhere along the gastrointestinal tract, most commonly in the stomach, duodenum, small bowel, and Meckel's diverticulum. Rarely, ectopic pancreatic tissue may be found in the gallbladder, omentum, umbilicus, colon, or lungs. The etiology of heterotopic pancreas is unclear. Aberrations in stem cell differentiation or migration of the pancreatic pouches during development are thought to be involved in this anomaly.

Heterotopic pancreas is usually an asymptomatic condition found incidentally at autopsy or surgery. Bowel obstruction may result when rests serve as lead points for intussusception or as space-occupying lesions. Other complications include hemorrhage and ulceration. Upper endoscopy is helpful in diagnosis. Submucosal nodules with central depression characteristic of heterotopic pancreas may be discerned. Biopsy is required to distinguish these lesions from polyps, leiomyomas, and lymphoma. Treatment is indicated for patients with complications from heterotopic pancreas. Excision with histologic examination is required to exclude malignancy.

### See Also the Following Articles

**Duodenal Obstruction • Duodenal Ulcer • Exocrine Pancreas • Pancreatitis, Acute • Pancreatitis, Chronic • Pancreatitis, Pediatric**

### Further Reading

Grendell, J. H., and Ermak, T. H. (1998). Anatomy, histology, embryology, and developmental anomalies of the pancreas. *In* "Sleisenger and Fordtrans's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, Management" (M. Feldman, B. Scharschmidt, M. Sleisenger, and R. Zoras, eds.), 6th Ed., pp. 761–770. W. B. Saunders Co., Philadelphia, PA.

Liddle, R. A. (1991). Congenital and hereditary diseases of the pancreas. *In* "Textbook of Gastroenterology" (T. Yamada, D. Alpers, C. Owyang, D. Powell, and F. Silverstein, eds.), 1st Ed., Vol. 2., pp. 1937–1942. J. B. Lippincott Co., Philadelphia, PA.

Oldham, K. (1997). Pediatric abdomen. *In* "Surgery: Scientific Principles and Practice" (L. Greenfield, M. Mulholland, K. Oldham, G. Zelenock, and K. Lillemoe, eds.), 2nd Ed., pp. 2038–2040. Lippincott-Raven, Philadelphia, PA.

Yeo, C. J., and Cameron, J. L. (2001). Exocrine pancreas. *In* "Sabiston Textbook of Surgery" (C. Townsend, R. Beauchamp, B. Evers, and K. Mattox, eds.), 16th Ed., pp. 1112–1114. W. B. Saunders Co., Philadelphia, PA.

# Pancreatic Bicarbonate Secretion

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**cholecystokinin** A peptide hormone produced by endocrine cells of the upper small intestine.

**vasoactive intestinal peptide** A polypeptide from the small intestine with cardiovascular and gastrointestinal effects.

**Following appropriate stimulation, the pancreas secretes a bicarbonate ($HCO_3^-$)-rich fluid that is derived largely from duct cells. Understanding how the pancreatic ductal epithelium is able to secrete $HCO_3^-$ at a concentration five- to sixfold greater than that in plasma is of intrinsic interest. Moreover, it is important from a clinical viewpoint: defects in ductal secretion underlie the pancreatic pathology that characterizes cystic fibrosis and perhaps certain forms of pancreatitis, whereas 90% of pancreatic cancers are of ductal origin.**

## INTRODUCTION

Pancreatic juice is the product of two distinct secretory processes: protein (enzyme) secretion and electrolyte secretion. Enzymes are secreted by exocytosis. Electrolyte secretion is achieved by the vectorial transport of ions across the secretory epithelium accompanied by water in isotonic proportions. The most significant of these ions is bicarbonate ($HCO_3^-$). Each day, these two secretory processes result in the human pancreas delivering 6–20 g of digestive enzymes to the duodenum in approximately 2.5 liters of $HCO_3^-$-rich fluid. Although the role of pancreatic enzymes is defined, that of pancreatic $HCO_3^-$ secretion is less precise. Clearly, the fluid acts as a vehicle for transporting enzymes to the duodenum where the $HCO_3^-$ neutralizes gastric acid. Pancreatic $HCO_3^-$ may also aid disaggregation of secreted enzymes following their exocytosis.

## PATTERNS OF BICARBONATE SECRETION

The regulation of pancreatic electrolyte secretion and the volume and composition of the secreted fluid differ considerably from species to species (Table I). It is important to recognize these differences for two reasons: (1) observations made in one experimental species, especially those involving models of disease, cannot be assumed to be relevant to humans; (2) a regulatory or secretory mechanism dominant in one experimental species may be present to a small, perhaps unrecognized, extent in humans where it could account for otherwise inexplicable symptoms and/or be explored therapeutically. The major differences and their relevance are as follows:

TABLE I Species-Dependent Patterns of $HCO_3^-$ Secretion

| Species | Stimulus | Volume | Maximum $[HCO_3^-]$ (mM) |
|---|---|---|---|
| Dog, cat, and human | Spontaneous | 0 (+) | — |
| | + Secretin | ++++ | 145 |
| | + CCK | + | 60 |
| | + Vagus | + | ? |
| Rat | Spontaneous | + | 25 |
| | + Secretin | + | 70 |
| | + CCK | +++ | 30 |
| | + Vagus | + | ? |
| Guinea pig | Spontaneous | + | 95 |
| | + Secretin | + | 150 |
| | + CCK | +++ | 140 |
| | + Vagus | +++ | 120 |

*Note.* This table gives an idea of the response to stimuli given alone; potentiation often occurs when stimuli are given together. Most data were obtained from studies on anesthetized animals; quantitative differences may occur in conscious animals, especially in the rat, in which secretion is increased fivefold in conscious animals. CCK, cholecystokinin.

1. In all species, secretin evokes the secretion of $HCO_3^-$-rich pancreatic juice. However, the amount of fluid that is secreted varies; an especially small amount is secreted in the rat (approximately fivefold less than that in cat, per gram of tissue). During maximal stimulation, $HCO_3^-$ concentration reaches

130 mmol/liter or more in all species except the rat, in which 70 mmol/liter is approximately the maximum value observed.

2. There is a reciprocal relationship between juice $HCO_3^-$ and $Cl^-$ concentrations: as flow rate increases, so does $HCO_3^-$ concentration, with a corresponding reduction in $Cl^-$ concentration. This reciprocal relationship results from a flow rate-dependent loss of $HCO_3^-$ from the primary secretion in exchange for $Cl^-$ as the fluid passes down the ductal tree.
3. The effect of cholecystokinin (CCK) on fluid secretion is very variable. In rat, it evokes a relatively large volume of $Cl^-$-rich fluid that is secreted by acinar cells. In guinea pig, it evokes a $HCO_3$-rich fluid. Studies on duct segments isolated from guinea pig pancreas indicate that the ducts are a source of this secretion, but do not exclude an acinar component. In other species, the effect of CCK lies somewhere between these two extremes. Where CCK is a weak stimulant of $HCO_3^-$ secretion, it usually potentiates the action of secretin.
4. The influence of vagal stimulation is also complex. In some species, muscarinic cholinoceptor activation evokes $HCO_3^-$ secretion. In some species (notably pig and guinea pig), vagal stimulation evokes a copious $HCO_3$-rich secretion because in these species the vagus nerves contain many VIPergic neurons and the vasoactive intestinal peptide released from these neurons acts in a manner similar to secretin.

In addition to these classical stimulatory mechanisms, many other candidate stimulatory and inhibitory control mechanisms undoubtedly influence pancreatic $HCO_3^-$ secretion to a greater or lesser extent.

## ORIGIN OF BICARBONATE SECRETION

Studies on isolated pancreatic duct segments confirm the generally held view, first proposed 50 years ago, that pancreatic duct cells are the principal site of $HCO_3^-$ secretion, without necessarily excluding a possible contribution from acinar cells. Given that duct cells constitute approximately 5% of gland mass, if all pancreatic fluid secretion was derived from duct cells, they would secrete their own volume of fluid in approximately 2 min. This assumes that all duct cells contribute equally to secretion. However, there is some evidence that the terminal duct cells (centroacinar cells) and small ducts contribute disproportionately to secretion, in which case the fluid secretory rate in that region is even faster.

## MECHANISM OF DUCTAL BICARBONATE SECRETION

The "textbook" model of $HCO_3^-$ secretion by pancreatic ducts has the following components: (1) generation of intracellular $HCO_3^-$ by the hydration of $CO_2$ under the influence of carbonic anhydrase; (2) extrusion from the cell of the residual protons by means of a $Na^+/H^+$ exchanger in the basolateral membrane; (3) secretion of $HCO_3^-$ across the apical (lumenal) membrane in exchange for $Cl^-$ on an anion exchanger working in parallel with an anion channel that allows entry of $Cl^-$ into the lumen. This lumenal anion channel is usually regarded as being the cystic fibrosis transmembrane conductance regulator protein (CFTR).

This model arose from early studies on perfused whole glands and, more recently (and more importantly), from experiments on isolated duct segments from rat pancreas. Although the model can successfully generate the $HCO_3^-$ concentrations observed in the rat (i.e., approximately 70 mmol/liter), on thermodynamic grounds it seems most unlikely to be able to generate the higher concentrations (up to 150 mmol/liter) seen in other species. However, recent observations have suggested a number of modifications to the model, which help to explain how the ducts of these species achieve such high secretory $HCO_3^-$ concentrations.

At the basolateral membrane, the situation is relatively clear. Although the $Na^+/H^+$ exchanger may be involved to a small extent in $HCO_3^-$ accumulation across the basolateral membrane, experimental studies on duct segments isolated from guinea pig pancreas show that it is largely achieved by a $Na^+-HCO_3^-$ co-transporter (NBC) located in this membrane. Furthermore, the electrogenicity of the NBC contributes to the driving force for $HCO_3^-$ secretion across the lumenal membrane. Immunohistochemical studies confirm that NBC is expressed in the basolateral membrane of human duct cells. However, since NBC is also present in rat ducts, its presence alone cannot account for the much higher $HCO_3^-$ concentrations secreted by the guinea pig pancreas.

At the lumenal membrane, the situation is less clear. Although spontaneous secretion in guinea pig ducts involves anion exchange across the lumenal membrane (Fig. 1A), secretin-evoked secretion can occur in the nominal absence of lumenal $Cl^-$ or when the activity of the anion exchanger is blocked. Furthermore, raising the lumenal $HCO_3^-$ concentration (as occurs during secretin stimulation) actually inhibits lumenal anion exchanger activity, thereby helping to prevent the reabsorption of secreted $HCO_3^-$. There must, therefore, be an

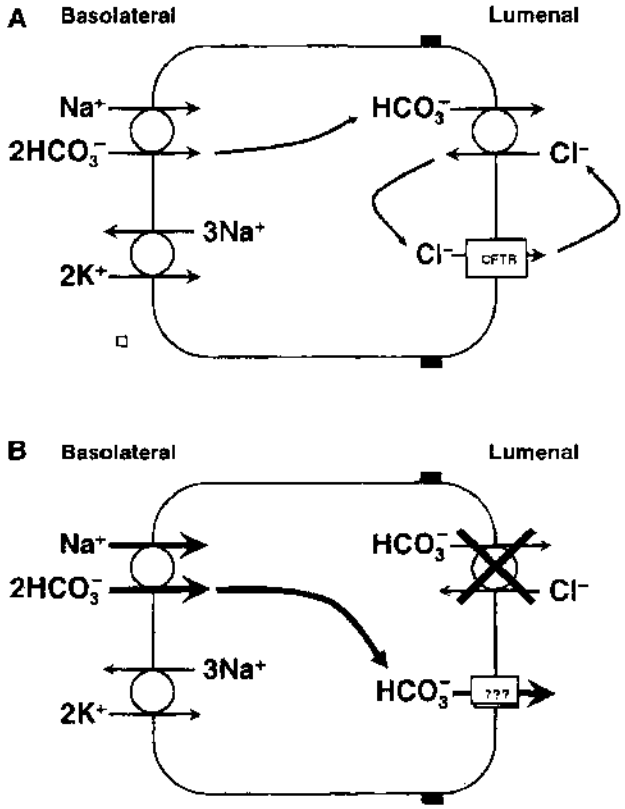


**FIGURE 1** $HCO_3^-$ secretion in guinea pig pancreatic duct. (A) During spontaneous secretion, $HCO_3^-$ enters the lumen by anion exchange with $Cl^-$, which recycles across the lumenal membrane via the CFTR $Cl^-$ channel. (B) Following stimulation with secretin, the anion exchanger becomes inhibited by the high lumenal $HCO_3^-$ concentration and $HCO_3^-$ secretion occurs mainly by diffusion through a lumenal anion channel, probably CFTR. In both situations, $HCO_3^-$ uptake across the basolateral membrane is achieved by $Na^+$–$HCO_3^-$ co-transport and, to a lesser extent, through $H^+$ extrusion by $Na^+/H^+$ exchange (not shown). Both processes derive their energy from the inward $Na^+$ gradient maintained by the basolateral $Na^+,K^+$-ATPase.

alternative pathway for $HCO_3^-$ secretion across the lumenal membrane under these conditions.

In contrast to its effect in rat ducts, secretin does not greatly depolarize cells in guinea pig ducts; instead the membrane potential remains at approximately −60 mV. Therefore, even at a lumenal $HCO_3^-$ concentration of 125 mmol/liter and a cytoplasmic $HCO_3^-$ concentration calculated to be 20 mmol/liter, the electrochemical gradient for $HCO_3^-$ would favor diffusion from the cell to the lumen via an anion channel. Furthermore, under these conditions intracellular $Cl^-$ dips to very low values (approximately 7 mmol/liter). Consequently, a $HCO_3^-$-rich secretion is favored by the lack of driving force for $Cl^-$ provided that the anion conductance at the lumenal membrane also conducts $HCO_3^-$ (Fig. 1B). Whether CFTR or another anion conductance provides such a pathway for $HCO_3^-$ remains to be clarified.

In other words, given a large enough $HCO_3^-$ conductance at the lumenal membrane and a low intracellular $Cl^-$ concentration, there may be no need to invoke any other membrane transport protein in the lumenal membrane to explain the high $HCO_3^-$ concentration observed in pancreatic juice from the guinea pig. If so, what is true for the guinea pig may presumably be true of other species, including humans, that show a similar pattern of $HCO_3^-$ secretion.

Finally, why does the rat not achieve such high $HCO_3^-$ concentrations? The answer may lie in the basolateral rather than the lumenal membrane. In rat (and mouse) ducts, fluid secretion can be inhibited by bumetanide. It thus seems likely that a $Na^+$–$K^+$–$2Cl^-$ co-transporter is present on the basolateral membrane of these species, which acts to increase intracellular $Cl^-$ concentration. As a result, there are driving forces for both $Cl^-$ and $HCO_3^-$ secretion via the lumenal anion conductance. This causes the production of a secretion containing comparable concentrations of the two anions. The absence or inactivity of this co-transporter in the guinea pig (and other species?) ensures that the secretion is $HCO_3^-$-rich.

## See Also the Following Articles

**Cholecystokinin (CCK) • Pancreatic Enzyme Secretion (Physiology) • Secretin • Vasoactive Intestinal Peptide (VIP)**

## Further Reading

Case, R. M. (1998). Pancreatic exocrine secretion: Mechanisms and control. *In* "The Pancreas" (H. G. Beger, *et al.*, eds.), pp. 63–100. Blackwell, Oxford.

Case, R. M., and Argent, B. E. (1993). Pancreatic duct secretion: Control and mechanisms of transport. *In* "The Pancreas: Biology, Pathobiology, and Disease" (G. L. W. Go, E. P. Di Magno, J. D. Gardner, E. Lebenthal, H. A. Reber, and G. A. Scheele, eds.), pp. 301–550. Raven Press, New York.

Ishiguro, H., Naruse, S., San Román, J. I., Case, R. M., and Steward, M. C. (2001). Pancreatic ductal bicarbonate secretion: Past, present and future. *J. Pancreas* 2, 192–197. Available at http://www.joplink.net.

Ishiguro, H., Steward, M. C., Sohma, Y., Kubota, T., Kitagawa, M., Kondo, T., Case, R. M., Hayakawa, T., and Naruse, S. (2002). Membrane potential and bicarbonate secretion in isolated interlobular ducts from guinea-pig pancreas. *J. Gen. Physiol.* 120, 617–628.

Sohma, Y., Gray, M. A., Imai, Y., and Argent, B. E. (2000). $HCO_3^-$ transport in a mathematical model of the pancreatic duct. *J. Membr. Biol.* 176, 77–100.

# Pancreatic Cancer

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**CA 19–9** Widely used serum marker for pancreatic cancer; has limited specificity because it is also expressed in other malignancies as well as in pancreatitis, hepatitis, and biliary obstruction.

**chemical splanchnicectomy** Chemical blockage of the celiac nerve plexus, performed either intraoperatively or percutaneously, in order to palliate pain associated with pancreatic adenocarcinoma.

**double duct sign** Dilation of the distal pancreatic and common bile ducts, with proximal stricturing of both structures evident on endoscopic retrograde cholangiopancreatography and highly suggestive of adenocarcinoma affecting the head of the pancreas.

**endoscopic ultrasonography** Imaging technique whereby an ultrasound probe attached to an endoscope is used to assess structures through the gastric and duodenal wall.

**gemcitabine** Chemotherapeutic agent and potent radiosensitizer that has recently been added to the multimodality treatment regimen for pancreatic adenocarcinoma.

**hereditary pancreatitis** Autosomal dominant trait, leading to recurrent acute pancreatitis and a 40-fold increased risk of pancreatic adenocarcinoma.

***K-ras*** Oncogene; the mutated form is found in over 90% of pancreatic cancers.

**laparoscopic staging** Minimally invasive means of evaluating the resectability of pancreatic adenocarcinoma by visualization through a tube inserted into the abdomen.

**neoadjuvant therapy** Strategy of preoperative administration of chemoradiation aimed at increasing the number of patients able to complete multimodality therapy.

**palliation** Treatment of symptoms such as abdominal pain to optimize quality of life, limit morbidity, and increase survival.

**pancreatic intraepithelial neoplasia** Areas of focal ductal proliferation adjacent to infiltrating pancreatic cancers that may be precursor lesions to pancreatic adenocarcinoma.

**pancreaticoduodenectomy** Surgical excision of the head and uncinate process of the pancreas by en bloc resection of the distal stomach and duodenum to the ligament of Treitz, common bile duct, and head of the pancreas. Also known as a Whipple procedure.

**Pancreatic adenocarcinoma is one of the deadliest known human malignancies, with an overall 5-year survival rate of less than 5%. Among gastrointestinal malignancies, pancreatic adenocarcinoma is second to colorectal cancer in terms of incidence in the United States, with 30,300 estimated new cases in 2002. Pancreatic cancer deaths in the United States in 2002 were estimated to approach 29,700, making pancreatic cancer the fifth most common cause of cancer-related mortality. Delayed diagnosis, relative chemotherapy and radiation resistance, and an intrinsic biologic aggressiveness all contribute to the abysmal prognosis associated with pancreatic adenocarcinoma. The risk of pancreatic adenocarcinoma is twice as great in men compared to women, and African Americans as well as Japanese Americans have a higher incidence compared to other ethnic groups, suggesting an as-yet undetermined specific genetic or environmental association.**

## EPIDEMIOLOGY

Many risk factors for pancreatic adenocarcinoma have been identified, with cigarette smoking having the strongest overall association and thought to account for one-quarter of all patients diagnosed. This may also in part explain the greater number of men diagnosed with pancreatic adenocarcinoma. The mechanism believed to be responsible for the association between cigarette smoking and pancreatic cancer involves the *N*-nitroso compounds present in cigarette smoke. Exposure to these agents leads to pancreatic ductal hyperplasia, a possible precursor to adenocarcinoma.

Other factors associated with increased risk of pancreatic adenocarcinoma include saturated fat intake, exposure to nonchlorinated solvents, and the pesticide dichlorodiphenyl trichloroethane (DDT), although the overall contribution of these is likely small. The risk of pancreatic adenocarcinoma increases with age, with most patients diagnosed between 60 and 80 years old. Studies examining the risk between alcohol consumption and pancreatic adenocarcinoma are equivocal, except in the case of heavy alcohol use leading to chronic pancreatitis. Chronic pancreatitis clearly increases the risk of pancreatic adenocarcinoma, although the direct or indirect role of alcohol is not yet defined.

 

supporting the hypothesis that they are precursor lesions. There appears to be a step-wise accumulation of specific genetic alterations in the continuum from normal tissue to infiltrating carcinoma, with mutations in K-ras and Her-2/neu occurring in low-grade lesions, mutations in p16 present in intermediate-grade lesions, and p53, DPC4, and BRCA2 mutations present in high-grade lesions. Although the progressive accumulation of genetic alterations has been identified, some controversy remains as to whether these lesions originate from fully differentiated duct cells or metaplastic conversion of either islet or acinar to ductal cells.

## CLINICAL PRESENTATION

The early symptoms associated with pancreatic adenocarcinoma are nonspecific and therefore patients often delay seeking medical attention until the disease is advanced. A common presenting symptom, present in over 90% of patients with pancreatic cancer, is cachexia, which usually precedes a diagnosis of pancreatic adenocarcinoma by many months. A major contributor to eventual mortality, cachexia is due to weight loss from local obstructive factors causing nausea, vomiting, and anorexia as well as to elaboration of tumor factors such as tumor necrosis factor α (TNFα) and cytokines such as interferon α (IFNα).

Abdominal pain is reported at presentation in 75–90% of patients with pancreatic cancer. The pain is believed to be caused by compression of, or invasion into, perineural and splanchnic neuronal structures as well as contiguous organs and the retroperitoneum. Because of the proximity of the common bile duct and duodenum to the pancreas, tumors located in the head of the organ may grow and compress these structures. Bile duct compression leads to obstructive jaundice in 70–85% of patients with pancreatic head lesions. Compression of the duodenum leads to delayed gastric emptying and early satiety, contributing to nausea and vomiting, which is initially present in 35–45% of patients. Up to 5% of patients present with advanced tumors causing complete duodenal obstruction.

The onset of diabetes mellitus is also associated with pancreatic adenocarcinoma, with 10–15% of patients developing glucose intolerance 6–12 months prior to cancer diagnosis. The onset of diabetes appears to be due to tumor elaboration of a yet undefined factor that stimulates islet cells to secrete the prodiabetic polypeptide amylin. Amylin levels are higher in patients with pancreatic adenocarcinoma compared to patients with diabetes and other gastrointestinal malignancies, and serum amylin levels and insulin resistance abate after tumor resection.

## DIAGNOSIS AND STAGING

Although the constellation of symptoms of abdominal pain, weight loss, nausea, vomiting, and obstructive jaundice is highly suggestive of pancreatic malignancy, other processes that can mimic these symptoms must also be considered. Benign biliary strictures and common bile duct stones as well as carcinoma of the bile ducts or gallbladder can cause these symptoms, as can ampullary and duodenal tumors. The possible diagnosis of pancreatic cancer is often proposed during the evaluation of obstructive jaundice by transabdominal ultrasonographic imaging. Because of multiple variables, including skill of the examiner, patient habitus, and overlying loops of gas-filled bowel limiting complete imaging, the sensitivity of transabdominal ultrasound for diagnosing pancreatic cancer has ranged from 44 to 94% in different studies. Even with optimal results, transabdominal ultrasound is not able to stage patients or determine resectablity, thus it must always be accompanied by another imaging modality.

Once a diagnosis of pancreatic cancer is suspected, the modality of choice for confirmation is a helical computed tomography (CT) scan of the abdomen with dual-phase scan acquisition. Dual-phase scans, acquired during both the arterial and the portal phases, allow for pancreatic parenchymal and arterial enhancement during the former phase, and hepatic parenchymal as well as peripancreatic venous enhancement during the later phase (Fig. 2). Enhancement of the pancreatic parenchyma allows for detection of small, hypodense

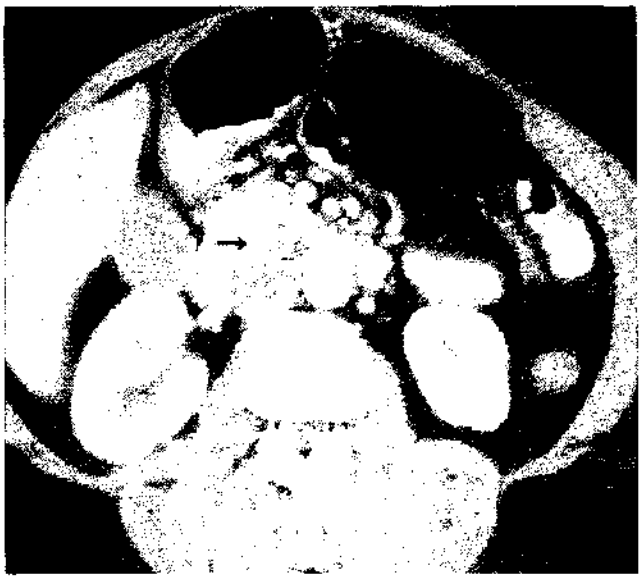

**FIGURE 2** Dual-phase computer tomography scan of a patient with a mass in the head of the pancreas (arrow) representing an adenocarcinoma.

carcinomas as well as arterial involvement by the tumor, which directly affects resectability and possible cure. Tumor involvement of venous vessels and liver metastasis are delineated during the portal phase. The sensitivity of helical CT scanning to detect lesions greater than 2 cm in diameter is approximately 89%, decreasing to approximately 71% for lesions less than 2 cm in diameter, with an overall diagnostic accuracy of 97% for pancreatic adenocarcinoma.

Besides providing a diagnosis, CT scanning is useful to determine resectability of the tumor. The criteria for resectability include absence of extrapancreatic disease, the absence of tumor extension to the superior mesenteric artery and celiac axis, and a patent superior mesenteric–portal vein confluence. The accuracy of CT for predicting unresectability approaches 100%, but the accuracy for predicting resectability is only approximately 30% due to the limited ability to detect small metastases to the surface of the liver, peritoneum, lymph nodes, and peripancreatic soft tissue.

Other modalities may be used to better define resectability prior to laparotomy. However, magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) offer no diagnostic advantage over CT, having an accuracy of 90–100% in several small series. The only role for magnetic resonance imaging in evaluating for potential pancreatic malignancy is in patients allergic to the iodinated contrast material used for CT imaging, because the contrast agent used, gadolinium, is associated with a lesser incidence of severe allergic reactions. Positron emission tomography (PET) scanning with fluodeoxyglucose F 18 offers promise for delineating inflammatory from neoplastic pancreatic processes, although experience is limited and data are unavailable for assessing overall accuracy.

Endoscopic ultrasonography (EUS) is highly sensitive for diagnosing pancreatic cancer, with an overall sensitivity of approximately 93% when combining data from various studies. EUS is particularly useful for detecting small (< 2 cm) pancreatic tumors that may not be well visualized by CT, as well as in assessment of local vascular involvement. Combining EUS with fine needle aspiration (FNA) of the tumor increases the specificity of EUS alone for diagnosing pancreatic cancer.

ERCP allows for visualization of the biliary and pancreatic ductal structures and may be useful for diagnosing the cause of biliary obstruction when no mass is evident by CT scanning, such as in ampullary tumors or cholangiocarcinoma, and for differentiating focal pancreatitis from neoplasm. Dilation of the distal pancreatic and common bile ducts with proximal stricturing of both structures, the "double duct sign," is highly suggestive of adenocarcinoma affecting the head of the pancreas (Fig. 3). Data summarized from 16 studies suggest that ERCP has a sensitivity of 92% and a specificity of 96% for diagnosing pancreatic cancer. Bile aspiration for cytologic evaluation and tissue sampling by biopsy and ductal brushing can also be performed at the time of ERCP. Biliary decompression can also be achieved at ERCP if a tumor has been deemed unresectable or if a patient with symptomatic biliary obstruction will have a delay prior to resection. Multiple studies have failed to show a benefit from routine preoperative biliary decompression, and some studies have shown increased operative morbidity related to infectious complications.

In addition to radiographic and endoscopic assessment, laparoscopy has been proposed as an accurate means of evaluation for resectability prior to laparotomy. Evaluation begins with a thorough inspection of the abdomen, including the liver and peritoneal surfaces. Any suspicious nodules should be biopsied for histological assessment. Metastatic disease not identified by spiral CT can be detected in as many as 30% of patients undergoing laparoscopic staging of pancreatic cancer. The addition of laparoscopic ultrasonography to evaluate for intrahepatic and lymph node metastasis as well as unrecognized vascular invasion may further alter the management of additional patients.

Because of the limitations of detecting very early pancreatic cancers, development of a biological marker that could detect these early lesions may translate into

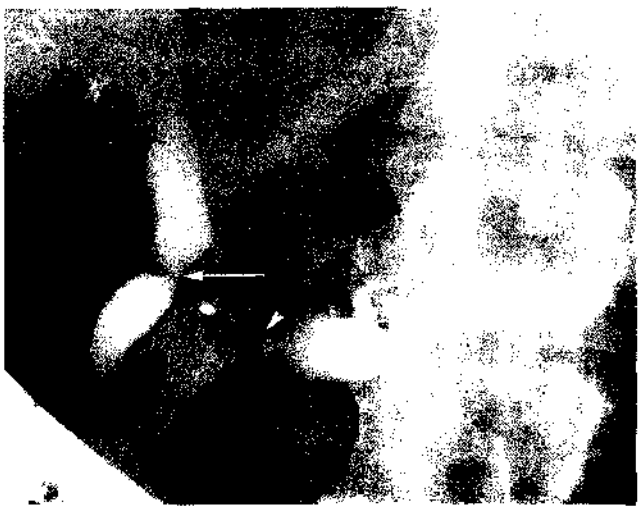

FIGURE 3 The "double duct sign." Endoscopic retrograde cholangiopancreatography of a patient with adenocarcinoma of the head of the pancreas reveals that both the common bile duct (arrow) and the pancreatic duct (arrowhead) are compressed by the tumor.

decreased mortality. Although many tumor markers have been investigated, currently none exists with acceptable specificity either for confirmation of pancreatic adenocarcinoma in equivocal cases or for routine screening.

CA 19-9 is presently the most widely used serum marker for pancreatic cancer. CA 19-9 is a sialylated Lewis[a] antigen associated with circulating mucins and is expressed in normal pancreatic, biliary, and gastric epithelial cells. Although it is most frequently elevated in pancreatic adenocarcinoma, it may also be expressed in biliary, gastric, and colonic malignancies as well as in acute and chronic pancreatitis, hepatitis, and biliary obstruction. Marked elevations are found in acute cholangitis and hepatic cirrhosis. The reported sensitivities and specificities of CA 19-9 for diagnosing pancreatic adenocarcinoma are related to the serum cutoff level selected. A cutoff of 15 U/ml produces a sensitivity of 92% and a specificity of 60%, whereas a cutoff of 1000 U/ml yields a sensitivity of 40% and a specificity of 99%. When using the usual cutoff of 37 U/ml, combined studies have shown a sensitivity of 81–85% and a specificity of 81–90%.

Carcineoembryonic antigen (CEA) is commonly used as a serum marker for colon cancer. It has been investigated as a marker for pancreatic adenocarcinoma, but its sensitivity and specificity from combined studies is 58 and 75%, respectively. A higher diagnostic accuracy of 83% is observed when measuring CEA levels in pancreatic juice rather than in serum. The oncogene *K-ras* is mutated in more than 90% of pancreatic adenocarcinomas and can be detected in the pancreatic juice from 55–77% of these patients. Several reports retrospectively examining pancreatic juice specimens from patients subsequently diagnosed with pancreatic adenocarcinoma have suggested that screening for *K-ras* mutations may be effective for the early detection of pancreatic cancer, but the utility of this is limited by the finding that *K-ras* mutations are also present in some cases of chronic pancreatitis. Whether *K-ras* mutations in the setting of chronic pancreatitis predict those who are at increased risk for developing pancreatic adenocarcinoma is currently unknown.

In some cases, even after multiple diagnostic modalities have been applied, it is still impossible to differentiate pancreatic adenocarcinoma from some other inflammatory process, often chronic pancreatitis, prior to laparotomy. In these instances, particularly when a pancreatic mass is identified in the setting of antecedent chronic pancreatitis, a tissue diagnosis is not necessary prior to resection. Although this approach risks overtreating a benign process, the greater concern is undertreating a potentially curable malignancy.

## SURGICAL TREATMENT

Only approximately 20% of pancreatic tumors are resectable at the time of diagnosis due to local vascular invasion in 40% of patients and metastatic disease present in 40%. Currently, the only potential cure for pancreatic adenocarcinoma is surgical resection. Because lesions originating in the head and uncinate process of the pancreas obstruct the bile duct and cause jaundice, they tend to present at an earlier stage and have a higher resectability rate than do cancers in the tail and body. The uncommon lesion in the pancreatic body or tail that is resectable may be treated by distal or subtotal pancreatectomy and splenectomy, whereas pancreatic head and uncinate lesions are treated by pancreaticoduodenectomy.

Although survival rates following pancreaticoduodenectomy are approximately 25% at 5 years with negative margins of resection, given the low postoperative mortality of 1–4% and the chance for cure, most patients with resectable disease and no prohibitive comorbidities undergo this operation. The procedure involves division of either the distal stomach, in the classic Whipple operation, or the proximal duodenum 2–3 cm distal to the pylorus in the pylorus-preserving modification, with en bloc resection of the distal common bile duct and involved portion of the pancreas along with the duodenum to the ligament of Treitz. Reconstruction consists of pancreatic, biliary, and either gastro- or duodenoenteric anastomoses, usually in that anatomical order. Typically, the proximal jejunum is used to reestablish pancreatic–enteric continuity, although the stomach is preferred by some surgeons, with roughly equivalent results.

Several important controversies surround the technical aspects of this operation. In Whipple's original description, the stomach was transected proximal to the antrum, whereas in the pylorus-preserving modification, the duodenum is transected 2–3 cm distal to the pylorus. The more extensive gastric resection was performed not only on oncologic grounds, but also to reduce the acid burden and subsequent incidence of marginal ulceration. Pylorus preservation maintains normal gastrointestinal physiology, specifically in terms of acid production, gastric reservoir and emptying functions, and hormone secretion. The rates of early postoperative delayed gastric emptying are similar for the two procedures, and pyloric preservation shortens operative time and is associated with no adverse early or late sequelae.

The extent of peripancreatic dissection is also the source of some controversy. The extended or radical pancreaticoduodenectomy entails en bloc wide

retroperitoneal lymphadenectomy and often resection of the superior mesenteric vein–portal vein confluence along with the tumor. Arguments that favor this approach claim improve resectability and cure rates, yet sufficient data are currently lacking to make a final determination. Although operative mortality rates associated with pancreaticoduodenectomy are typically 1–4%, up to half of the patients undergoing this operation will experience a complication. Approximately 30% of patients undergoing a pancreaticoduodenectomy will experience delayed gastric emptying, though to be related to decreased motilin levels, removal of the duodenal pacemaker and disruption of gastroduodenal neural connections. Erythromycin, a motilin agonist, has been found to improve gastric emptying of both solids and liquids when administered intravenously during the postoperative period.

Pancreatic fistula resulting from failure of healing at the pancreatic–enteric anastomosis, with subsequent intraperitoneal leakage of pancreatic secretions, can usually be managed conservatively if there is no evidence of abdominal sepsis. Isolated fluid collections should be drained, percutaneously if possible, and the patient should have nutrition provided parenterally and remain without oral intake. Intraoperatively, a drain is usually placed in the vicinity of the pancreatic–enteric anastomosis and should be maintained as the fistula is allowed to heal.

Intraabdominal abscesses can result from leakage at the pancreatic–enteric, gastroenteric, or hepaticoenteric anastomoses. Patients with evidence of systemic infection should be evaluated for an intraabdominal abscess and the collection should be drained, preferably percutaneously, with the initiation of appropriate antibiotics. In addition, hepaticoenteric anastomotic leaks may require a transhepatic catheter to allow for external biliary drainage.

## PALLIATION OF UNRESECTABLE PANCREATIC ADENOCARCINOMA

At the time of diagnosis, 80% of patients are not candidates for potentially curative resection, narrowing their options to medical palliation for the primary disease and treatment of specific complications of pancreatic cancer. The majority of patients diagnosed with pancreatic adenocarcinoma will experience one or more of its complications, including biliary obstruction, gastric outlet obstruction, and severe abdominal pain. As well, with improvements in determining preoperative resectability of pancreatic cancer, fewer patients undergo exploratory laparotomy during which palliative procedures are performed. Palliation of the complications of pancreatic cancer may be achieved nonsurgically in most cases.

Up to 70% of patients with pancreatic cancer will develop obstructive jaundice and accompanying pruritis with an increased risk of cholangitis. In patients deemed unresectable intraoperatively, a biliary -enteric bypass may be performed for decompression. The preferred procedures involve hepatico- or choledocojejunostomy; cholecystoenterostomy is associated with a rate of recurrent jaundice of 20%. In patients deemed unresectable who do not undergo an operation, endoscopic or transhepatic radiographic placement of a biliary stent may be accomplished. Radiographically placed transhepatic catheters with exclusive external biliary drainage result in large fluid and electrolyte losses and are less desirable for palliation of obstructive jaundice in patients with pancreatic cancer. This procedure is reserved for patients who fail internal endoscopic drainage. Biliary decompression prior to planned resection should be limited to cases with severe symptoms of obstructive jaundice in which surgery is delayed.

Gastric outlet obstruction from duodenal compression will affect up to 25% of patients with pancreatic cancer and may require surgical gastric bypass for palliation. Controversy exists as to whether patients deemed unresectable at exploratory laparotomy should undergo a prophylactic gastroenteric bypass. Proponents cite the higher mortality rate, approaching 25%, for patients requiring a second operation for palliation of gastric outlet obstruction following exploratory laparotomy, as well as no increase in mortality when gastric bypass is performed at the initial operation. Increased morbidity associated with gastric bypass, most notably delayed gastric emptying, as well as increased hospital stay and overestimation of the need for gastric bypass at the time of exploration is cited by its opponents. A confounding factor in the discussion of pancreatic cancer-related gastric outlet obstruction is whether common symptoms of nausea and vomiting represent gastroparesis or true mechanical obstruction. Clearly, any patient with radiographically confirmed gastric outlet obstruction associated with pancreatic adenocarcinoma who is fit for surgery should undergo gastroenterostomy, using either an open or laparoscopic technique. Limited data are available regarding the use of endoscopically deployed duodenal stents in this setting.

Severe, debilitating abdominal pain and back pain are a frequent complication of pancreatic

adenocarcinoma, often requiring significant analgesia for adequate palliation. Chemical splanchnicectomy with 50% ethanol, performed either at the time of exploration or subsequently through the percutaneous route, has been shown to palliate pain associated with pancreatic adenocarcinoma, although its duration is limited. When performed intraoperatively, this procedure has not been accompanied by increases in morbidity, mortality, return to oral intake, or length of hospital stay.

Thoracoscopic splanchnectomy, using video-assisted thoracoscopy, transects the pain fibers in the posterior mediastinum as they course cephalad through the sympathetic chain. The short-term efficacy is clear, with 99% of patients reporting excellent analgesia and 50% reporting a sustained effect at 4 months. This procedure does involve a general anesthetic, a hospital stay, and an associated risk of complications that occur more often and are more severe compared to chemical splanchnicectomy. The role of palliative radiotherapy for pain control has been used, but has several limitations, including extended length of time for pain control to be achieved and need for repeated hospital visits.

For the 80% of patients deemed unresectable, palliative chemoradiation has been shown to increase survival and possibly to reduce severity of pain compared to untreated patients. In 1981, the Gastrointestinal Tumor Study Group (GITSG) published results of a trial in which patients surgically staged to confirm unresectability and no evidence of peritoneal or liver metastases were randomized to receive either external beam radiation alone or external beam radiation with 5-fluorouracil (5-FU). Patients treated with chemoradiation fared better in terms of median survival (49 weeks) than did those receiving radiation alone (22 weeks). Other studies have confirmed the benefit of multimodality therapy over either radiotherapy or chemotherapy alone. In a subsequent GITSG trial, patients received either combined streptozotocin, mitomycin C, and 5-FU (SMF) alone or radiotherapy with 5-FU followed by SMF. The median survival in patients receiving chemoradiation was 42 weeks, compared with 32 weeks in those assigned to the chemotherapy alone group, and 1-year survival was 41% in the chemoradiation group and 19% in the SMF alone group.

A recent advance in the chemotherapeutic regimen to treat pancreatic adenocarcinoma is the use of gemcitabine, a potent radiosensitizer. Gemcitabine has been shown to improve survival when compared to 5-FU, with reported 1- year survival rates of 18 and 2%, respectively. As well, gemcitabine appears to confer clinical benefit in terms of decreased pain intensity and analgesic consumption with improvement in overall functional status.

## NEOADJUVANT THERAPY

The observation that 25–30% of patients do not receive adjuvant therapy following pancreatic resection due to prolonged recovery, perioperative complications, or patient refusal has led to the investigation of preoperative chemoradiation. Besides increasing the number of patients able to complete multimodality therapy, neoadjuvant therapy has been studied for its ability to convert locally unresectable pancreatic cancer to resectable disease. Other advantages of this modality include more effective radiation therapy to well-oxygenated cells not devascularized by surgery, reducing tumor dissemination during surgical manipulation, and targeting retroperitoneal margins of excision that may not be adequately treated surgically. As well, preoperative chemoradiation would allow an interval window for restaging prior to surgical resection so that previously occult metastatic disease could be detected, thus saving patients an unnecessary laparotomy. The utility of this approach is currently under intense investigation.

## ADJUVANT THERAPY FOR RESECTABLE PANCREATIC ADENOCARCINOMA

The basis for adjuvant therapy following surgical resection with negative margins comes from a GITSG study that showed a median survival nearly twice as long for patients treated postoperatively with radiation and concurrent 5-FU compared to those randomized to observation alone (20 vs. 11 months, respectively). Single-institution studies investigating the benefit of postoperative chemoradiation compared to observation have also shown a survival benefit. Thus, the current data support the use of postoperative adjuvant chemoradiation in patients who undergo surgical resection.

## FUTURE STRATEGIES

Although many recent advances have been made in the treatment of pancreatic adenocarcinoma, including lower postoperative mortality rates, neoadjuvant therapy, and addition of gemcitabine to the multimodality armamentarium, none is expected to dramatically alter the high mortality associated with this disease. The single advance that offers the most promise is elucidation of the molecular events involved in pancreatic oncogenesis, metastasis, and resistance to radiation and chemotherapy.

Understanding pancreatic adenocarcinoma on a molecular level allows for the development of targeted therapies that may be employed either alone or in combination with traditional chemoradiation. The finding that the *K-ras* oncogene is mutated and activated in over 90% of pancreatic adenocarcinomas, and that this is an early event in the accumulation of genetic damage, has prompted investigation into strategies that would block its activation. SCH 66336, a farnesyl transferase inhibitor that renders *K-ras* functionally inactive, as well as *K-ras* antisense therapy, are currently being investigated.

The p53 tumor suppressor is often mutated and functionally inactive in pancreatic adenocarcinoma, causing inhibition of a major apoptotic pathway induced by most chemoradiation therapies. Strategies to correct functional losses are more challenging than are those that inhibit gene expression or function, but one promising method is to use genetically modified adenoviruses that replicate only in p53-deficient cells. An additional challenge for pancreatic cancer is delivering the virus to the tumor target, although intratumoral injection using endoscopic ultrasound is an area of investigation. Other molecular therapeutic targets are angiogenic factors such as vascular endothelial growth factor (VEGF), which is up-regulated in pancreatic adenocarcinoma, growth stimulatory factor receptors such as the epidermal growth factor receptor and human growth factor receptor 2 (HER2), as well as matrix metalloproteinases that degrade the extracellular matrix, allowing cancer cells to metastasize. Strategies to antagonize these factors and their function have been developed and are currently being tested in clinical trials. Although the prognosis of pancreatic adenocarcinoma remains abysmal, the outlook for novel molecular strategies that would significantly reduce the mortality and suffering associated with this disease is very promising.

## See Also the Following Articles

**Cancer, Overview • Computed Tomography (CT) • Pancreatic Ductal Adenocarcinoma • Pancreatic Tumors, Other • Pancreatitis, Hereditary • Smoking, Implications of**

## Further Reading


Barkin, J., and Goldstein, J. (1999). Diagnostic approach to pancreatic cancer. *Gastroenterol. Clin. North Am.* 28, 709–722.

Evans, D. (2001). Preoperative chemoradiation for resectable and locally advanced adenocarcinoma of the pancreas. *J. Gastrointest. Surg.* 5, 2–5.

Freeny, P. (1999). Pancreatic imaging: New modalities. *Gastroenterol. Clin. North Am.* 28, 723–746.

Jemal, A., Thomas, A., Murray, T., and Thun, M. (2002). Cancer statistics, 2002. *CA Cancer J. Clin.* 52, 23–47.

Kern, S. (2000). Molecular genetic alterations in ductal pancreatic adenocarcinomas. *Med. Clin. North Am.* 84, 691–695.

Kern, S., Hruban, R., Hollingsworth, M., Brand, R., Adrian, T., Jaffee, E., and Tempero, M. (2001). A white paper: The product of a pancreas cancer think tank. *Cancer Res.* 61, 4923–4932.

McGinn, C., and Zalupski, M. (2001). Combined-modality therapy in pancreatic cancer: Current status and future directions. *Cancer J.* 7, 338–348.

Sener, S., Fremgen, A., Menck, H., and Winchester, D. (1999). Pancreatic cancer: A report of treatment and survival trends for 100,313 patients diagnosed from 1985–1995, using the National Cancer Database. *J. Am. Coll. Surg.* 189, 1–7.

Sohn, T., Lillemoe, K., Cameron, J., Huang, J., Pitt, H., and Yeo, C. (1999). Surgical palliation of unresectable periampullary adenocarcinoma in the 1990s. *J. Am. Coll. Surg.* 188, 658–666.

Wolff, R. (2001). Novel therapies for pancreatic cancer. *Cancer J.* 7, 349–358.

Yeo, C. (1999). The Whipple procedure in the 1990s. *Adv. Surg.* 32, 271–303.

# Pancreatic Digestive Enzymes

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**translational control** The regulation of protein synthesis at the level where the mRNA sequence is translated into the amino acid sequence on the ribosome.
**zymogen granules** Pancreatic acinar cell secretory granules.
**zymogens** Inactive precursors of certain pancreatic digestive enzymes that are activated by proteolytic cleavage.

**The pancreatic digestive enzymes are a mixture of approximately 20 enzymes synthesized by pancreatic acinar cells and secreted into the pancreatic ducts. These enzymes are responsible for almost all of the activity during the lumenal phase of digestion in the intestine.**

## INTRODUCTION

Pancreatic digestive enzymes can be divided into four groups according to the major class of macronutrients upon which they act (Table I). There is only one major form of amylase, DNase, and RNase, possibly due to the relatively limited number of distinct chemical bonds to cleave. There is a much more diverse array of proteases, due to the increased complexity of peptide bonds as a result of the larger number of amino acids. Multiple closely related forms, termed isoenzymes, are present for many proteases, such as trypsinogens 1, 2, and 3. The biological significance of these multiple gene products is not clear. All of the pancreatic proteases, as well as phospholipase A2 and colipase, are synthesized as inactive precursors known as zymogens and designated by either the prefix "pro" or the suffix "ogen." These have little or no enzymatic activity in the pancreatic juice but are activated in the intestinal lumen by a cascade in which the intestinal enzyme enterokinase cleaves and activates trypsinogen and the released trypsin rapidly activates the other enzymes. This article addresses the general features of pancreatic digestive enzymes.

**TABLE I Human Pancreatic Digestive Enzymes**

| Enzyme | Molecular weight (daltons) |
|---|---|
| Proteases | |
| Trypsinogen 1 | 25,000 |
| Trypsinogen 2 | 25,000 |
| Trypsinogen 3 | 23,400 |
| Chymotrypsinogen | 24,000 |
| Proelastase 1 | 33,000 |
| Proelastase 2 | 26,600 |
| Kallikreinogen | 35,000 |
| Procarboxypeptidase A1 | 44,500 |
| Procarboxypeptidase A2 | 47,000 |
| Procarboxypeptidase B1 | 47,300 |
| Procarboxypeptidase B2 | 47,300 |
| Glycosidase | |
| Amylase | 57,000 |
| Lipases | |
| Triglyceride lipase | 48,000 |
| Colipase | 10,000 |
| Carboxyl ester hydrolase | 100,000 |
| Phospholipase A2 | 14,000 |
| Nucleases | |
| DNase 1 | 30,000 |
| RNase | 15,000 |

## SYNTHESIS AND PACKAGING OF DIGESTIVE ENZYMES

All of the digestive enzymes contain a sequence in the nascent peptide that induces translation on ribosomes attached to the endoplasmic reticulum (ER). The nascent peptide is inserted through a protein channel into the lumen of the ER. There the proteins are processed and folded with the help of intralumenal chaperone proteins. The proenzymes move to the Golgi by vesicular transport and in the *trans*-Golgi network are sorted into newly forming secretory granules, termed condensing vacuoles, which are distinguishable in electron microscopic images by their lower density. With the possible help of granule membrane proteins, such as GP-2, the contents become more densely packed and lose some of their water. Mature zymogen granules then move from the Golgi to the apical region of the cell in a microtubule-dependent manner, where they await the signal for exocytosis, the process by which their contents are released into the acinar lumen. Although the concept was somewhat controversial in the past, all the different digestive enzymes synthesized in each cell are believed to be packaged in the same granules. When granules differ in enzyme content, it is believed to be due

 

to different levels of mRNA being expressed in different cells. For example, the acinar cells surrounding the islets of Langerhans have larger amounts of certain enzymes such as amylase, possibly due to locally high concentrations of insulin. The stimulation of secretion from such different regions of the gland can result in the phenomenon of "nonparallel secretion," in which the composition of secreted digestive enzymes changes in response to a physiological stimulus.

## REGULATION OF DIGESTIVE ENZYME SYNTHESIS BY DIET AND HORMONES

The synthesis of digestive enzymes is regulated at several levels. Dietary adaptation occurs when the pancreas modifies its composition of different digestive enzymes in response to changes in the level of dietary protein, fat, and carbohydrate. In general, enzyme levels increase in response to an abundance of their specific dietary substrate. Thus, a high-starch diet induces the presence of more amylase and a high-protein diet induces the presence of more proteases. This effect takes 2–10 days to occur and is accompanied by changes in mRNA levels for the individual digestive enzymes. Some of these effects are well established as being hormonally mediated. Thus, insulin, which increases in response to a high-carbohydrate diet, increases amylase mRNA levels through enhanced gene transcription. Cholecystokinin (CCK) has similarly been related to a high-protein diet and secretin to a high-fat diet. These changes have been studied primarily in rodents and their relevance to the human pancreas is unknown.

The second type of regulation is the increased rate of protein synthesis due to enhanced mRNA translation that occurs following a meal. In this case, because mRNA levels are relatively unchanged, synthesis of all the digestive enzymes increases in parallel and the main function is to increase the amount of new enzyme in the cell to be ready for the next meal. This effect is mediated by the pancreatic secretagogues, CCK and acetylcholine (the latter is released from the vagal nerve), insulin, and dietary amino acids, particularly branched chain amino acids such as leucine. These all activate a biochemical pathway that involves protein kinase B (Akt) and mTOR (mammalian target of rapamycin) and leads to the activation, by phosphorylation or dephosphorylation, of specific translation factors and ribosomal proteins that are involved in the initiation and elongation stages of translation.

### See Also the Following Articles

**Amylase • Digestion, Overview • Pancreatic Enzyme Secretion (Physiology) • Pancreatic Triglyceride Lipase • Trypsin**

### Further Reading

Adelson, J. W., and Miller, P. E. (1989). Heterogeneity of the exocrine pancreas. *Am. J. Physiol.* **256**, G817–G825.

Lowe, M. E. (1993). The structure and function of pancreatic enzymes. *In* "Physiology of the Gastrointestinal Tract" (L. R. Johnson, ed.). 3rd Ed., pp. 1531–1542. Raven Press, New York.

Scheele, G. A. (1993). Extracellular and intracellular messengers in diet-induced regulation of pancreatic gene expression. *In* "Physiology of the Gastrointestinal Tract" (L. R. Johnson, ed.), 3rd Ed., pp. 1543–1554. Raven Press, New York.

Williams, J. A. (2001). Intracellular signaling mechanisms activated by cholecystokinin regulating synthesis and secretion of digestive enzymes in pancreatic acinar cells. *Annu. Rev. Physiol.* **63**, 77–97.

# Pancreatic Disease, Pediatric

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**acute pancreatitis** An acute condition due to inflammatory disease of the pancreas that typically presents with abdominal pain and elevated pancreatic enzymes in the blood.

**chronic pancreatitis** A persistent inflammatory disease of the pancreas characterized by irreversible morphological change that often causes pain or loss of exocrine function or both.

**exocrine pancreas** The portion of the pancreas that synthesizes and secretes the components of pancreatic juice. The juice contains digestive enzymes, water, and bicarbonate. The pancreatic acinar and ductal cells constitute the cellular components of the exocrine pancreas.

**pancreatic insufficiency** Decreased secretion of digestive enzymes or insulin to the extent that malabsorption or diabetes mellitus appears. Malabsorption typically manifests with steatorrhea, the presence of more than 7% of dietary fat in the stool.

**Disorders of the exocrine pancreas represent a small segment of pediatric disease, but are common enough that all physicians caring for children should have a working knowledge of the pancreatic diseases that affect children. Cystic fibrosis is the most common ailment of the exocrine pancreas in children, but there are many other causes of pancreatic dysfunction and inflammation in pediatrics that present difficult diagnostic challenges. This article focuses on the disorders of the exocrine pancreas that affect children except for the pancreatic dysfunction associated with cystic fibrosis.**

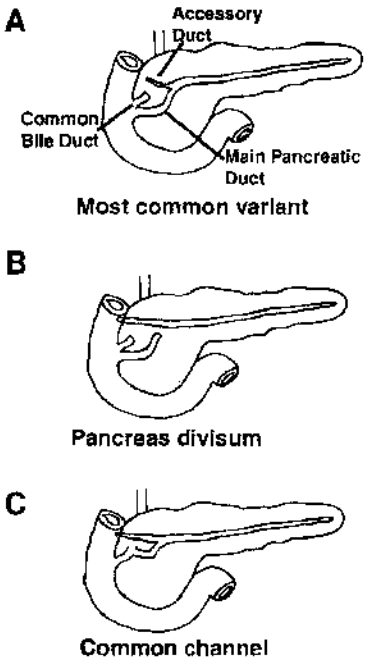


**FIGURE 1** Three variations in ductal anatomy. (A) In 40–50% of people, the main pancreatic duct enters the duodenum with the common bile duct and the accessory duct regresses. (B) Five to 10% of people have pancreas divisum. The main and accessory pancreatic ducts do not connect and each duct drains into the duodenum through its own papilla. (C) The main pancreatic duct enters the common bile duct approximately 5 to 15 mm before the ampulla of Vater in approximately 5 to 10% of individuals.

## CONGENITAL ANOMALIES

### Pancreas Divisum

Incomplete fusion of the dorsal and ventral pancreas may result in the substitution of the dorsal pancreatic duct, which empties through the relatively small accessory papilla, for the ventral duct as the main conduit for pancreatic fluids (Fig. 1). This anatomical variant, pancreas divisum, is the most common congenital anomaly of the pancreas and the most controversial. Some believe that an anatomic or functional stenosis at the accessory papilla produces increased ductal pressure, which, in turn, causes bouts of acute and recurrent pancreatitis. Others point out that there is no causal relationship between pancreas divisum and pancreatitis and that there is disagreement among clinical studies about the incidence of pancreatitis in patients with pancreas divisum. Some studies have found an increased incidence, whereas other studies have failed to confirm those findings.

The diagnosis of pancreas divisum is best made by endoscopic retrograde cholangiopancreatography (ERCP). The role of magnetic resonance cholangiopancreatography (MRCP) has not been established in pediatric patients. Once pancreas divisum is diagnosed,

 

the decision to treat, and how to treat, is not straightforward. If the patient has had recurrent episodes of pancreatitis, most gastroenterologists opt for ERCP therapies, such as sphincterotomy with or without stenting, particularly if objective evidence of papillary stenosis exists. Rarely, a surgical drainage procedure is offered.

### Common Channel Syndrome

Abnormal junctions of the common bile duct and the main pancreatic duct represent another frequently encountered ductal anomaly. In these cases, the common bile duct joins the main pancreatic duct 5 to 15 mm before the ampulla of Vater to create a common channel, which has been associated with pancreatitis, choledochal cysts, and, in adults, bile duct or gallbladder cancer. Because the juncture occurs before the sphincter of Oddi, bile can reflux into the main pancreatic duct and cause pancreatitis. Similarly, pancreatic juice can reflux into the common bile duct, a situation that may cause some choledochal cysts. Animal models support both relationships. The presentation of these patients relates to the symptoms of pancreatitis or of choledochal cysts. The latter presents with right upper quadrant pain, jaundice, and, sometimes, a palpable mass below the liver. The diagnosis can be made by ERCP, MRCP, or intraoperative cholangiogram. Treatment for choledochal cysts is excision of the cysts with a Roux-en-Y hepatojejunostomy. Therapy for an isolated common channel has traditionally been surgical, but, recently, ERCP treatments have been advocated although long-term studies of outcome after ERCP therapy are lacking.

### Annular Pancreas

Annular pancreas is an uncommon developmental anomaly that is generally associated with other congenital malformations and has a particularly high incidence in patients with trisomy 21. The exact pathogenesis of annular pancreas remains unclear although most theories invoke a failure in one of the steps leading to fusion of the ventral and dorsal pancreatic buds. Symptoms of partial or complete upper gastrointestinal obstruction present at any age, but newborns represent the largest group. Radiographic studies, such as upper gastrointestinal series, ultrasound, and ERCP, can suggest the diagnosis of annular pancreas, but definitive diagnosis occurs at surgery. During surgery, the obstruction is bypassed by a duodenoduodenostomy or duodenojejunostomy.

### Pancreatic Agenesis and Aplasia

Disorders of pancreatic development are rare and range from complete to partial agenesis of the pancreas. Only two cases of pancreatic agenesis and five cases of partial agenesis were described in an autopsy series of 2000 fetuses. These disorders almost certainly arise from mutations in the genetic or signaling pathways responsible for the early development of the fetal pancreas. In one patient with pancreatic agenesis, a homozygous mutation in the PDX1 gene was identified. PDX1 is a transcription factor that is required for pancreatic development in rodents and almost certainly contributed to the lack of pancreatic development in this patient.

Complete absence of the pancreas is incompatible with life and is usually diagnosed at autopsy. Newborns with this disorder have significant intrauterine growth retardation and insulin-dependent hyperglycemia. In contrast, most cases of partial pancreatic agenesis remain asymptomatic and may be diagnosed at surgery or autopsy. Only those with less than approximately 5% of normal tissue will manifest evidence of exocrine dysfunction with poor growth and fat malabsorption or evidence of endocrine dysfunction with hyperglycemia and low glucagon levels and response. With treatment of the endocrine insufficiency with pancreatic enzymes and fat-soluble diets and insulin if required, these patients may do well.

## HEREDITARY DISORDERS

### Shwachman–Diamond Syndrome

Shwachman–Diamond syndrome (SDS) is the second most commonly recognized cause of pancreatic insufficiency in children. Estimates of incidence for this autosomal recessive disease range from 1 in 10,000 to 1 in 50,000 live births. Although the constellation of pancreatic insufficiency and hematological abnormalities in the face of normal sweat electrolytes typifies this disorder, many other organ systems may be affected (Table I). Among these, the prominent features include short stature, skeletal abnormalities, and learning or behavioral abnormalities.

The pancreas varies in size from normal to small and has a prominent fatty infiltration, which replaces acinar tissue and can be appreciated in computed tomography of the abdomen. The ducts appear normal and pancreatic secretions have relatively normal volume with normal levels of bicarbonate and chloride. The primary defect is in the acinar cells and may involve a defective transcription factor or growth factor, which would also account for the wide range of organ involvement in SDS

TABLE I Features of Shwachman–Diamond Syndrome

| |
|---|
| Pancreatic exocrine insufficiency |
| Short stature |
| Hematological changes |
| Neutropenia |
| Thrombocytopenia |
| Anemia |
| Myelolymphoproliferative disorders |
| Skeletal changes |
| Metaphyseal chondrodysplasia |
| Short or flared ribs |
| Clinodactyly |
| Delayed bone age |
| Recurrent infections |
| Liver changes |
| Elevated serum aminotransferases |
| Periportal fibrosis |
| Miscellaneous |
| Psychomotor retardation |
| Ichthyosis |
| Dental abnormalities |

Linkage studies suggest that the defective gene or genes locate in the peri-centrometric region of chromosome 7. At present, a specific gene has not been identified.

Most patients present in infancy with symptoms of pancreatic insufficiency. Interestingly, pancreatic exocrine function improves with age and as many as 50% of patients have normal fecal fat excretion by 4 years of age. Even so, these patients still have decreased secretion of pancreatic enzymes in pancreatic stimulation tests. This is also true of the patients who do not have steatorrhea. Analysis of pancreatic secretions in this group still reveals deficient secretion of pancreatic enzymes but at levels that permit efficient digestion of dietary fats. Thus, normal fecal fat excretion does not exclude the diagnosis of SDS.

Likewise, the bone marrow dysfunction, generally neutropenia, anemia, or thrombocytopenia, is not always found initially. Both the neutropenia and thrombocytopenia can be intermittent and multiple blood counts should be performed to aid diagnosis. The anemia is less common than the other two abnormalities and is often mild. Bone marrow biopsies in patients with SDS vary considerably and may be normal or show decreased cellularity, fat infiltration, and myeloid maturation arrest.

Therapy is symptomatic and includes optimal pancreatic enzyme replacement, fat-soluble vitamin supplementation, and aggressive treatment of febrile episodes, particularly during periods of neutropenia. Even with optimal treatment, SDS patients may not reach normal adult height. Growth hormone therapy does not appear to alter this outcome. Complications of bone marrow failure produce the most morbidity and mortality in SDS. Infections may be life-threatening in patients with neutropenia, and myelodysplasia, aplastic anemia, and acute myeloid leukemia may be significantly increased in SDS patients.

### Johansson Blizzard Syndrome

This syndrome also causes pancreatic lipomatosis, but it is considerably less common than SDS, with fewer than three dozen cases described. Like SDS, the exocrine pancreatic insufficiency in this syndrome most likely results from a defect in acinar cell development, whereas duct function remains intact. In addition to exocrine pancreatic insufficiency, the syndrome includes imperforate anus, hypoplastic alae nasi, hypothyroidism, ectodermal scalp defects, deafness, and mental retardation. Other endocrine abnormalities and genitourinary defects have also been described. Unlike SDS, this syndrome does not include hematological or skeletal abnormalities.

### Pearson's Marrow–Pancreas Syndrome

Described in 1979, this syndrome consists of refractory sideroblastic anemia with vacuolization of erythroid and myeloid precursors. The described patients all required repeated blood transfusions and all had failure to thrive. With increased age, many organs, such as the liver, kidney, intestine, skin, and nervous system, show abnormalities. The patients who survived infancy underwent pancreatic stimulation testing, which showed deficient secretion of digestive enzymes, decreased volume, and low bicarbonate concentrations, indicating defects in both acinar and duct cell function in distinction from SDS. At autopsy, fibrosis and acinar cell atrophy were found. Fatty infiltration was not present. Mutations, often deletions, in mitochondrial DNA have been consistently found in patients with this syndrome. The connection between mutations in mitochondrial DNA and pancreatic dysfunction has not been established, but may relate to impaired energy production in the pancreas, which must meet the high energy requirements required to produce large amounts of proteins.

### Jeune Syndrome

Pancreatic insufficiency, abnormalities of the thorax, short-limbed dwarfism, cystic dysplasia of the kidneys, and hepatic portal lesions characterize this rare syndrome. The skeletal abnormalities in the thorax may

produce respiratory distress in neonates. Fibrosis and cystic lesions are found in the pancreas.

## Isolated Enzyme Deficiencies

A small number of papers report patients with deficiencies of individual pancreatic digestive enzymes and of enterokinase, an intestinal brush-border enzyme that is required for activation of pancreatic zymogens. The patients with decreased levels of triglyceride lipase or of colipase, an essential cofactor for triglyceride lipase, all had evidence of fat malabsorption that was improved by pancreatic enzyme supplementation. These patients presented with oily bowel movements, but otherwise had no other symptoms and were well grown. In contrast, the two reported patients with decreased trypsin activity presented with severe growth failure, hypoproteinemia, and edema. Although the authors speculated that the patients had trypsin deficiency, the report lacked any supporting evidence for a defect in trypsin. A later report of patients with identical clinical symptoms and similarly decreased protease levels raised additional questions about the existence of isolated trypsin deficiency. In these patients, enterokinase was deficient in small bowel biopsies, endogenous enterokinase corrected the protease deficiencies, and the symptoms resolved with pancreatic enzyme supplementation. No gene defects have been described in patients with any of these purported deficiencies and until that time the existence of these isolated enzyme deficiencies is uncertain.

## Hereditary Pancreatitis

First described in 1952, hereditary pancreatitis is a rare disorder causing recurrent episodes of acute pancreatitis and, in approximately 75% of patients, chronic pancreatitis. Multiple pedigrees have been well described and it is clear that hereditary pancreatitis has an autosomal dominant inheritance pattern with approximately 80% penetrance and a variable clinical course even among family members.

Recently, mutations in the cationic trypsinogen gene were linked to the development of hereditary pancreatitis in most kindreds. Two mutations, R122H and N29I, are the most prevalent and have been described in families from North America, Europe, and Japan. A few patients have other substitutions at these same amino acid positions. Additional mutations in the same gene, A16V, D22G, and K23R, have been described in a small number of patients, but these are weakly associated with pancreatitis.

The mechanism behind the increased incidence of pancreatitis in patients with mutations in the cationic trypsinogen gene remains speculative. After the description of the R122H mutation, it was speculated that the mutation interfered with the normal protective mechanisms of the acinar cells against premature activation of trypsinogen (Fig. 2). Intracellular activation of trypsinogen would permit the activation of other zymogens,

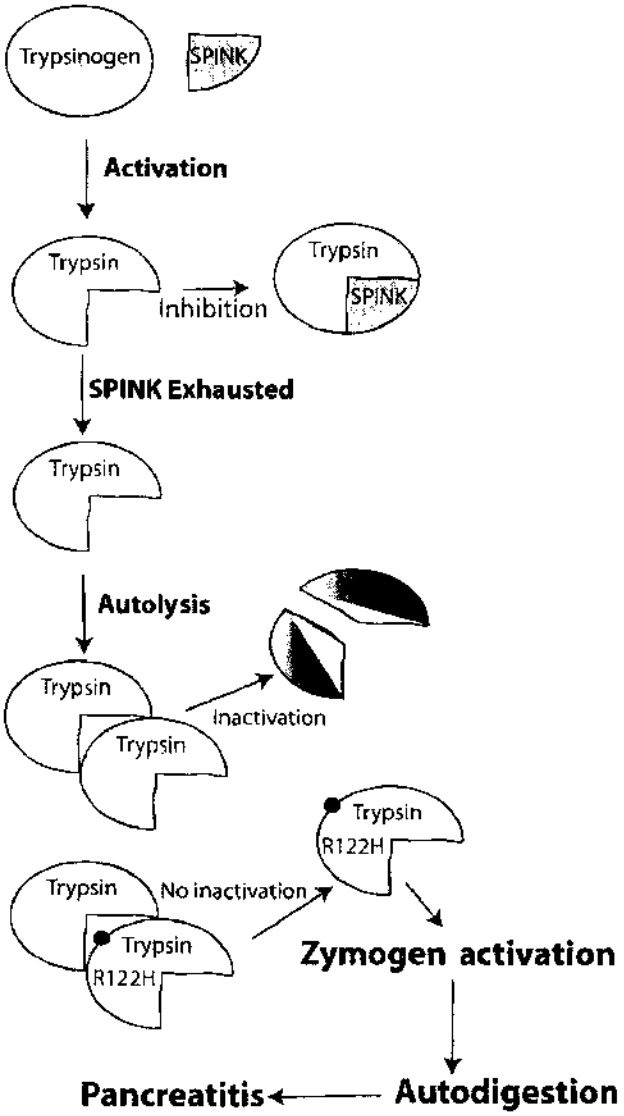


**FIGURE 2** Mechanisms that protect the pancreas from premature trypsinogen activation. Acinar cells synthesize and package trypsinogen and SPINK1 or pancreatic secretory trypsin inhibitor at a 5 to 1 ratio. When trypsinogen is activated to trypsin, the first line of defense is inhibition by SPINK1. If there is enough trypsinogen activation to overwhelm the capacity of SPINK1, then trypsin autolysis provides a second line of defense. Autolysis begins with cleavage of the bond after arginine 122. In hereditary pancreatitis, the R122H mutation slows autolysis and allows trypsin to activate other zymogens. Once the zymogen activation cascade begins, autodigestion of the pancreatitis can occur and produce pancreatitis.

resulting in damage to the acinar cells. To protect against premature trypsinogen activation, the acinar cell contains an inhibitor of trypsin. This first line of defense is limited and can be overwhelmed by excessive trypsin activation. In that case, the acinar cell has a second line of defense, trypsin autolysis. Degradation begins with hydrolysis at Arg-122. In hereditary pancreatitis, the histidine substitution at position 122 prevents autolysis. *In vitro* studies on human cationic trypsinogen confirm the increased autolytic resistance of the R117H mutant and also demonstrate that the mutation interferes with multiple protective mechanisms. For instance, the mutation increases trypsinogen autoactivation. Similar studies on the R29I human cationic trypsinogen reveal that the mutation results in faster autoactivation and increased trypsin stability. Thus, both mutants can increase the trypsin levels in the acinar cells and cause increased activation of other zymogens.

Episodes of pancreatitis begin before the age of 20 in approximately 80% of patients. Pain is generally the presenting symptom and may be accompanied by nausea and vomiting. Although some authors suggest that fasting, fatty meals, alcohol, and stress may precipitate pancreatitis, the triggers for individual episodes remain ambiguous, despite the considerable progress made in understanding the pathophysiology of hereditary pancreatitis in the past 5 years. The attacks occur with variable frequency and may become less frequent and less severe with age, but this progression is not universal.

With time, the pancreas atrophies and calcifications develop in approximately 50% of patients. Pancreatic insufficiency develops in a sizable proportion of patients, perhaps as many as 75%. Diabetes mellitus is also relatively common. In some, glucose intolerance may be more troublesome during episodes of pancreatitis. As in other causes of pancreatitis, pseudocysts and hemorrhage can complicate the clinical course. Importantly, the risk of pancreatic cancer is increased above that for the general population and the cumulative risk may be 40% by age 70. The incidences of these complications have not been clearly established, in part because, until recently, identification of patients was limited to clinical diagnoses.

Treatment of acute episodes is supportive, as discussed later. Little can be done to prevent episodes. If triggers for acute pancreatitis are identified, they should be avoided. In most patients, the triggers are elusive. Even so, patients should be advised to avoid alcohol and medications known to cause pancreatitis. Antioxidant cocktails have been suggested as a way to prevent attacks, but no study has demonstrated clear benefit. Regular monitoring for complications is an important facet of patient management. Patients who develop pancreatic insufficiency should receive pancreatic enzyme and fat-soluble vitamin supplementation. Some may require insulin. Chronic pain develops in many patients and presents difficult management decisions. Narcotic analgesia may be required for long periods of time. Treating structural complications may relieve pain in some patients. Pseudocysts can be observed over time for spontaneous resorption or they may require drainage (Fig. 3). Currently, endoscopic internal drainage and external drainage by interventional radiologists offer viable options to surgery. The chronicity, size, location, and complexity of the pseudocyst all contribute to decisions about the best treatment. Generally, pancreatic duct strictures and pancreatic stones can be treated by balloon dilation and stent placement during ERCP. In some patients, surgical drainage procedures, such as a modified Puestow (longitudinal pancreaticojejunostomy), are performed in an attempt to relieve chronic pain. The success of these procedures is difficult to assess because available reports group hereditary pancreatitis with other forms of chronic pancreatitis.

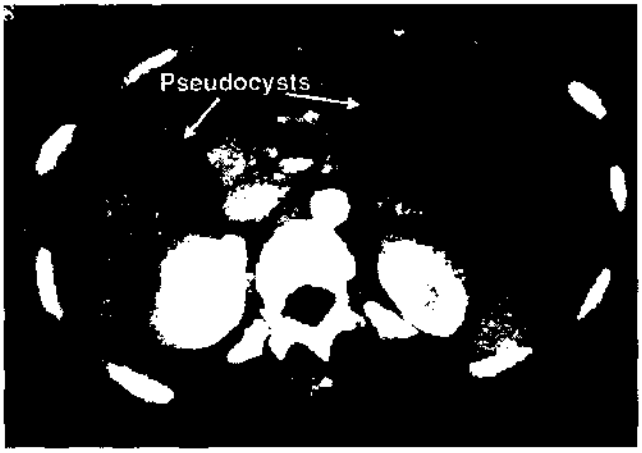


FIGURE 3 Pancreatic pseudocysts. Fluid collections are common complications of acute and chronic pancreatitis. Larger collections may persist and develop a pseudomembrane. These collections can become infected, obstruct other organs, and be a source of hemorrhage.

## ACUTE PANCREATITIS

Pancreatitis in children is not common, although the true incidence has never been reliably determined. Earlier published series reported 2 to 9 cases per year in each institution. A more recent series from a large children's hospital shows a steady increase in incidence from 5 cases per year to 113 cases per year 5 years later. Whether this change represents an actual increase in incidence or in diagnosis is uncertain.

TABLE IV Complications of Acute Pancreatitis

| Local | Systemic |
|---|---|
| Edema | Shock |
| Inflammation | Pulmonary edema |
| Fat necrosis | Pleural effusions |
| Phlegmon | Acute renal failure |
| Hemorrhage | Coagulopathy |
| Abscess | Hypocalcemia |
| Fluid collections | Hyperglycemia |
| Extension to nearby organs | Distant fat necrosis |

except that abnormal attenuation, rather than altered echogenicity, is seen. If the pancreas does not perfuse with intravenous contrast during the CT scan, pancreatic necrosis is likely. MRCP may be helpful in defining abnormalities of the ductal system, but its utility in pediatric patients has not been carefully studied. ERCP should be reserved for patients with unexplained recurrent episodes of pancreatitis, a prolonged episode of pancreatitis, or gallstone pancreatitis.

Medical management of acute pancreatitis is supportive and consists of providing adequate fluids and analgesia and of monitoring for metabolic complications (Table IV). Nutritional therapy should be started early in the hospitalization. Until recently, parenteral nutrition was considered the only option, but several studies show that adult patients with acute pancreatitis tolerate jejunal feeding with fewer complications than those given parenteral nutrition.

Fortunately, pancreatitis is generally not severe in children. Hemorrhagic pancreatitis and infected pancreatic necrosis can occur, but the incidence has not been adequately established. Hypovolemic shock and severe underlying systemic illness are risk factors for severe pancreatitis in children. Typically, patients with severe pancreatitis develop ominous clinical findings such as peritoneal signs, respiratory distress, or circulatory collapse. The utility of either the Ranson or APACHE II scoring system for the severity of pancreatitis has not been tested in pediatrics. The prophylactic use of broad-spectrum antibiotics in severe pancreatitis remains an unsettled issue because current evidence supporting this approach has many uncertainties and leaves unanswered a number of questions about details of therapy. Still, many clinicians would commence a course of broad-spectrum antibiotics in critically ill patients. Surgical debridement is rarely required in children, but should be considered in patients with necrosis who are deteriorating or failing to progress despite maximal supportive care.

Other complications of pancreatitis may require specific treatment. Pancreatic pseudocysts occur frequently in children and are managed as discussed earlier. Abscesses can often be treated with external drainage and intravenous antibiotics and surgical drainage is rarely necessary. Surgery may be necessary for traumatic rupture of the duct although endoscopic stenting across the disrupted duct is another option.

## CHRONIC PANCREATITIS

The distinction between acute and chronic pancreatitis may present diagnostic problems, particularly in the early stages of chronic pancreatitis. To make a diagnosis of chronic pancreatitis, irreversible morphological changes in the pancreas must be present. These changes are most often determined by radiographic studies or by ERCP (Fig. 4). The presence of permanent exocrine insufficiency and diabetes mellitus in association with the morphological changes greatly aids the diagnosis. Patients with recurrent pancreatitis that is secondary to ductal obstruction may show radiographic changes similar to those seen in chronic pancreatitis and may even have evidence of decreased function, but these can improve on correction of the obstruction.

In pediatrics, cystic fibrosis is by far the commonest cause of chronic pancreatitis. Other causes, hereditary pancreatitis and SDS, have been discussed. The remaining causes occur quite infrequently. Many cases remain idiopathic despite advances in the diagnosis of genetic and structural defects. In a few affected patients, biopsy of the pancreas reveals marked fibrosis of the parenchyma with relative sparing of islets. This entity has been called juvenile idiopathic fibrosing pancreatitis and may lead to pancreatic or bile duct obstruction by fibrotic tissue. Other identifiable causes of chronic pancreatitis include hyperparathyroidism (in which the hypercalcemia is thought to cause repeated episodes of pancreatitis) and hyperlipidemias, in particular types I, IV, and V. Tropical pancreatitis is found only in tropical areas including south India and Africa and its etiology remains unknown. Autoimmune pancreatitis causes chronic pancreatitis associated with increased serum gamma globulin, autoantibodies, enlargement of the

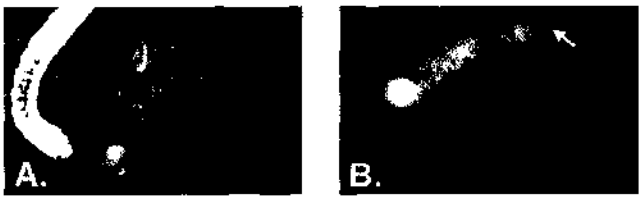


FIGURE 4 ERCP in chronic pancreatitis. (A) Normal ductal anatomy is visualized by contrast injection. (B) The dilated and tortuous main pancreatic duct in a patient with chronic pancreatitis. A stricture is present near the tail (arrow).

pancreas, which may be diffuse or localized, and a narrow main pancreatic duct. Although rare, the diagnosis is important because these patients respond to steroid therapy. To date, there have been no reports of autoimmune pancreatitis in children. The diagnosis and treatment of childhood chronic pancreatitis are the same as discussed for hereditary pancreatitis.

## See Also the Following Articles

**Cystic Fibrosis • Exocrine Pancreatic Insufficiency • Pancreatitis, Acute • Pancreatitis, Chronic • Pancreatitis, Hereditary • Pancreatitis, Pediatric**

## Further Reading

Durie, P. R., Forstner, G. G., Gaskin, K. J., Kopelman, H. R., Pitchumoni, C. S., and Robertson, M. A. (1996). The pancreas. *In* "Pediatric Gastrointestinal Disease" (P. R. Durie, J. R. Hamilton, W. A. Walker, J. A. Walker-Smith, and J. B. Watkins, eds.), 2nd Ed., Vol. 2, pp. 1247–1513. Mosby, New York.

Lopez, M. J. (2002). The changing incidence of acute pancreatitis in children: A single-institution perspective. *J. Pediatr.* 140, 622–624.

Storman, M. O., and Durie, P. R. (2002). Pathophysiologic basis of exocrine pancreatic dysfunction in childhood. *J. Pediatr. Gastroenterol. Nutr.* 35, 8–21.

Werlin, S. L. (1998). Disorders of the pancreas in children. *Curr. Opin. Pediatr.* 10, 507–511.

# Pancreatic Ductal Adenocarcinoma

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**adenocarcinoma** Malignant neoplasm of epithelial origin that is predominantly glandular or ductal.

**ascites** the accumulation of free fluid in the peritoneal cavity.

**Blumer's shelf** Palpable rectovaginal or rectovesical nodularity that may represent metastatic disease from an intra-abdominal or retroperitoneal malignancy.

**carcinomatosis** The presence of widespread peritoneal implants from tumor.

**cholangitis** Infection of the biliary tract.

**Courvoisier's sign** A nontender, palpable gallbladder, often associated with a malignant obstruction of the common bile duct.

**double duct sign** A radiographic sign seen on computed tomography scan or endoscopic retrograde cholangiopancreatography that results from the simultaneous obstruction of the common bile duct and pancreatic duct by a mass from the head of the pancreas.

**endoscopic retrograde cholangiopancreatography** A method of cholangiography that involves cannulating the sphincter of Oddi under direct vision through a fiberoptic endoscope.

**endoscopic ultrasound** A method of ultrasound performed via an endoscope that can be useful in evaluating the presence and character of a gastric, duodenal, biliary, or pancreatic mass.

**gastric outlet obstruction** A clinical condition that consists of epigastric abdominal pain, early satiety, and postprandial emesis that can be associated with, but is not specific to, pancreatic malignancy.

**gastric varices** Dilated gastric veins that occur as a result of portal hypertension; may also occur as a result of splenic vein thrombosis.

**jaundice** Yellowish discoloration of the skin.

**oncogene** The altered form of a proto-oncogene that promotes uncontrolled cell proliferation.

**proto-oncogene** Cellular genes that are involved in the regulation of proliferation, development, and differentiation.

**Sister Mary Joseph's nodule** Periumbilical mass that may contain lymph node metastases from a peritoneal source of malignancy.

**steatorrhea** Excess fecal fat, which may be a manifestation of pancreatic exocrine insufficiency and fat malabsorption.

**Trousseau's sign** Recurrent or migratory superficial thrombophlebitis that may be an early manifestation of abdominal cancer or other systemic illnesses.

**tumor suppressor gene** Altered form of anti-oncogene whose loss-of-function or deactivation has a permissive role in the development of a neoplasm.

**Virchow's node** Lymph node located at the terminus of the thoracic duct in the left supraclavicular region that may contain lymph node metastases from distant primary sites via the retroperitoneal and postmediastinal lymph channels.

**Pancreatic ductal adenocarcinoma is a malignancy of the exocrine pancreas that is the fifth leading cause of cancer-related deaths. Although the exact cause of this disease is unknown, factors thought to contribute its etiology include cigarette smoking and other environmental risks. The molecular mechanisms involved in the pathogenesis of these tumors include mutations in the K-ras oncogene, p53 and DPC4 tumor suppressor genes, and the p16 cell cycle regulatory protein. The clinical symptoms of pancreatic cancer include jaundice, abdominal pain, and weight loss. There is often a delay in diagnosis that contributes to the high rate of mortality resulting from the disease. Newer diagnostic and staging modalities involve the use of tumor markers, helical computed tomography scanning, magnetic resonance imaging, endoscopic ultrasound, and laparoscopy. If the tumor is localized to the pancreas, surgical resection offers the only chance of long-term cure. Adjuvant chemoradiation strategies can improve survival and decrease local recurrence. In advanced disease, palliation of obstructive jaundice, gastric outlet obstruction, and pain is important.**

## INTRODUCTION

In the United States, pancreatic cancer (ductal adenocarcinoma) accounts for approximately 30,000 deaths per year. The majority of patients present in the late stages of the disease with locally advanced or metastatic tumors. Only 10–20% of patients are candidates for resection and hence have any potential for cure. The signs and symptoms of pancreatic cancer vary from vague nonspecific abdominal complaints to severe jaundice and often the diagnosis can be difficult, especially in the early stages. Until the past decade or so, the traditional approach was surgical exploration for tissue diagnosis, staging, and assessment of resectability. More recently, sophisticated tests, including thin-cut helical computed tomography (CT) scan, magnetic resonance imaging (MRI), endoscopic ultrasound (EUS), biochemical tumor markers, fine-needle aspiration (FNA) cytology, and laparoscopy, have added a new dimension to the diagnosis and staging of pancreatic carcinoma. The treatment of pancreatic cancer is surgical resection, when possible. Adjuvant chemoradiation has been shown by several, but not all, studies to improve survival. The overall prognosis for these patients depends on pathologic variables of the tumor. Future strategies for earlier diagnosis and treatment are focused on the evolving knowledge of the genetic mutations that characterize pancreas cancer.

## EPIDEMIOLOGY AND ETIOLOGY

Cancer of the pancreas is distinctly more common in older people with most patients between the ages of 65 and 80 at diagnosis. There is a slight male predilection for the disease with the male to female ratio being 1.3 to 1.0. The strongest association is between pancreatic cancer and cigarette smoking. Current estimates suggest that 30% of pancreatic cancer cases are due to cigarette smoking. A high-protein and high-fat diet, characteristic of the Western population, has been proposed as a possible factor. Exposure to industrial carcinogens, especially betanaphthylamine and benzidine, has been documented in pancreatic cancer patients. A higher that normal incidence rate of the neoplasm has also been reported in chemists, workers in metal industries, and coal and gas plant employees.

Diabetes mellitus has been proposed as a risk factor for pancreatic cancer. However, a large cohort study examining this issue showed that the diabetes was typically of new onset, indicating that it was brought on by the tumor. Another known risk factor is longstanding chronic pancreatitis. Such patients have a 1.8 and 4.0% chance of developing pancreatic cancer 10 and 20 years, respectively, after their initial diagnosis of chronic pancreatitis. Finally, pancreatic cancer is associated with certain inherited diseases, such as the atypical mole melanoma syndrome and hereditary pancreatitis.

## PATHOLOGY AND MOLECULAR BIOLOGY

Most (95%) malignant neoplasms of pancreatic origin arise from the exocrine portion of the gland, with ductal adenocarcinomas being the most common subtype. The predominant histologic feature of these tumors is a dense collagenous stroma with atrophic acini, remarkably preserved islet cell clusters, and a slight to moderate increase in the number of ducts, both normal-appearing and cancerous (Fig. 1). The diagnosis of ductal adenocarcinoma rests on the identification of mitoses, nuclear and cellular pleomorphism, discontinuity of ductal epithelium, and evidence of perineural, vascular, or lymphatic invasion. Much more infrequent are tumors arising from the islets of Langerhans (endocrine cells

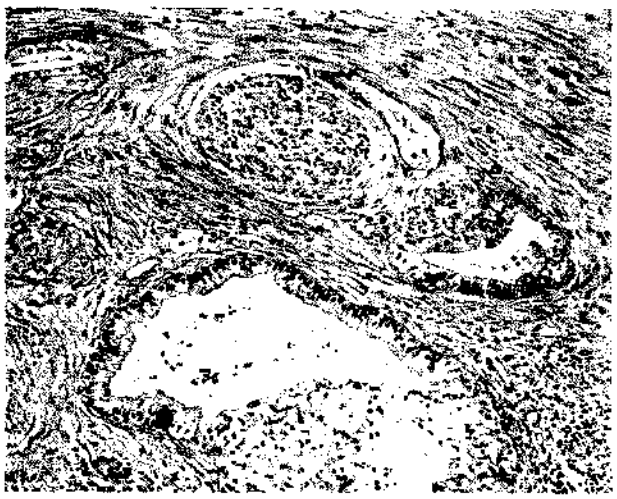

FIGURE 1 Hematoxylin and eosin section of pancreatic ductal adenocarcinoma. Note extensive fibrosis and perineural invasion.

of the pancreas). Primary nonepithelial tumors of the pancreas (e.g., lymphomas or sarcomas) are extremely rare.

Sporadic cancers of the pancreas are frequently associated with the activation of an oncogene, K-ras, and the inactivation of multiple tumor suppressor genes, including p53, *DPC4* (deleted in pancreatic carcinoma, locus 4), p16, and Rb. Up to 90% of human pancreatic cancers have ras gene mutations, most of which are K-ras mutations, and K-ras mutations seem to be an early event in pancreatic carcinogenesis. A number of studies have indicated that p53 mutations are relatively common in adenocarcinoma of the pancreas, occurring in 70% of patients. In addition, p53 mutation may be an independent prognostic factor in patients with pancreatic ductal adenocarcinoma. Mutations in the p16 gene are found in approximately 60% of pancreatic adenocarcinomas and may be associated with short patient survival. *DPC4* is inactivated in approximately half of all pancreatic cancers and, in contrast to p53 and p16, appears to be relatively specific to pancreatic cancer.

## CLINICAL PRESENTATION

The clinical features of pancreatic cancer vary from vague symptoms of abdominal discomfort to anorexia, weight loss, and obstructive jaundice (Table 1). The initial symptoms and signs depend on the site and extent of the pancreatic cancer. Not surprisingly, tumors of the pancreatic body and tail can grow to a very large size before obvious symptoms alert the patient or physician to the diagnosis. On the other hand, small tumors, when located in the pancreatic head, can cause obstructive jaundice or "pancreatitis," alerting the clinician to suspect pancreatic cancer.

Progressive jaundice occurs in over 75% of patients with carcinoma of the head of the pancreas and the incidence of jaundice decreases as the location of the lesion progresses to the left toward the tail of the pancreas. Occasionally, a tumor may invade and compress the third or fourth part of the duodenum without actually obstructing the common bile duct. This is often seen in cancer originating in the lower part of the uncinate process that tends to extend inferiorly into the root of the superior mesenteric vessels. Pain is extremely frequent and the classic description of painless jaundice is rarely encountered. Weight loss and anorexia are also common symptoms even in early stages. Nausea, epigastric bloating, change in bowel habits, and vomiting are occasionally present. Hematemesis and melena may sometimes occur in late cases as a result of direct invasion into the duodenal or gastric mucosa by tumor or portal vein–splenic vein compression by the tumor, leading to gastric varices. Chills and fever due to ascending cholangitis rarely occur even in longstanding biliary obstruction unless the biliary tree is contaminated by catheterization at endoscopic retrograde cholangiopancreatogram (ERCP).

Physical examination may not be pathognomonic but may aid in the diagnosis. Approximately 75% of patients with carcinoma of the head of the pancreas are jaundiced. The palpable gallbladder (Courvoisier's sign) may be present in 25% of patients with a malignant obstruction of the common bile duct. Patients with advanced disease may present with ascites, palpable supraclavicular lymphadenopathy (Virchow's node), a periumbilical mass (Sister Mary Joseph's nodule), or a palpable rectovaginal or rectovesical nodularity (Blumer's shelf). Diabetes of recent onset in elderly

TABLE 1 Signs and Symptoms of Pancreatic Cancer

| |
|---|
| Jaundice |
| Pain |
| Weight loss |
| Anorexia |
| Nausea |
| Bloating |
| Emesis |
| Courvoisier's gallbladder |
| Diabetes of recent onset |
| Advanced disease |
| Ascites |
| Virchow's node |
| Sister Mary Joseph's nodule |
| Blumer's shelf |
| Trousseaus's sign (migratory thrombophlebitis) |

patients with vague gastrointestinal symptoms should alert the physician to a possible underlying pancreatic carcinoma. Migratory thrombophlebitis (Trousseau's sign) can be present in any patient with advanced cancer, is not specifically indicative of pancreatic carcinoma, and, by itself, does not merit diagnostic laparotomy or laparoscopy.

## DIAGNOSIS AND STAGING

It is clear that no clinical feature by itself is sufficiently accurate to make a definite diagnosis of, or to exclude, a pancreatic cancer. The following list should serve as a guideline to choose those patients who may warrant further investigation of the pancreas. The clinical suspicion should be increased in patients who are over 40 years of age, who are heavy cigarette smokers, and who present with any of the following symptoms: (1) obstructive jaundice; (2) unexplained recent weight loss greater than 10% of body weight; (3) unexplained upper abdominal or lumbar back pain; (4) unexplained dyspepsia; (5) sudden onset of diabetes mellitus without any predisposing factors, such as a family history of diabetes mellitus or obesity; (6) one or more attacks of "idiopathic" pancreatitis; and (7) unexplained steatorrhea. It should be remembered that the earlier the cancer, the more difficult it is to achieve a positive diagnosis, even at operation.

### CA 19-9 and Other Tumor Markers

CA 19-9 was first described in 1979 as a tumor-associated antigen and later identified as a Lewis blood group-related mucin. Although initially CA 19-9 was thought to be useful in the management of patients with colorectal carcinoma, its role in pancreatic cancer became more evident. Over the past 10 years, several hundred papers have subsequently documented the utility of CA 19-9 in the diagnosis, prognosis, and monitoring of pancreatic cancer. However, as is the case with most tumor markers, the sensitivity of CA 19-9 is not perfect. Therefore, the proper role for CA 19-9 is as a diagnostic adjunct or simply as another piece of critical diagnostic information to be integrated into the diagnostic decision-making process.

When CA 19-9 reference values of >90 or >200 U/ml are used, the diagnostic accuracy for pancreatic cancer is 85 or 95%, respectively. However, there are several factors that influence CA 19-9 interpretation, most importantly the degree of jaundice. The false increase is likely because of hepatic insufficiency to degrade and excrete CA 19-9 metabolically. Additionally, CA 19-9 levels can be elevated in other tumor types, such as lung and ovarian cancers. Even in severe cases of pancreatitis, high CA 19-9 levels are noted. Interferon significantly elevates CA 19-9. Finally, patients with the Lewis blood phenotype (-a, -b) and pancreatic cancer may not have elevated levels of CA 19-9. The combined use of CT and CA 19-9 in nonicteric patients provides a positive predictive value of 99 to 100% in the diagnosis of pancreatic cancer when a reference value of 100 U/ml is used. Likewise, better results are obtained if CA 19-9 is used in conjunction with ultrasound or ERCP. A host of other tumor markers, such as CA 125, CEA, CA 494, CA 242, CA 50 SPAN-1, DU-PAN 2, and CA12–5, have been described for detection of pancreatic adenocarcinoma. Although some of these markers appear promising, most of them are not widely available and have not been tested to same degree as CA 19-9.

### Ultrasonography

Real-time ultrasonography is an excellent modality for the initial evaluation of upper abdominal pain or obstructive jaundice. It does not entail exposure to ionizing radiation and is less costly and time consuming than CT scan. However, 15 to 20% of ultrasound examinations are technically suboptimal, as a result of bowel gas interference, obesity, or previous operations. Furthermore, visualization of the body, tail, and uncinate process is often marginal. Bile duct dilation defined as greater than 7 mm is commonly seen with carcinoma of the pancreatic head. However, bile duct dilation is not specific for carcinoma and may be indicative of advancing age, prior cholecystectomy, common duct stones, ampullary stenosis, and pancreatitis. Pancreatic ductal dilation, defined as ductal diameter exceeding 2 to 3 mm, is one of the most frequent secondary signs, seen in 20 to 60% of cases of pancreatic cancer. Most pancreatic cancers are hypoechoic relative to the normal parenchyma, whereas an increase in echogenicity may be found in focal pancreatitis. Ultrasonography is also useful in the detection of ascites and liver metastases. The yield of ultrasonography depends mostly on the skill of the ultrasonographer and thus may vary from institution to institution.

### Computed Tomography Scanning

Thin-section helical CT scanning through the pancreas with an intravenous bolus injection of contrast remains the test of choice to evaluate the extent of disease in pancreatic cancer and to assess tumor resectability (Fig. 2). Typical CT findings of pancreatic cancer are those of a mass that deforms the size and contour of the gland. Most tumors have a central area of decreased attenuation (hypodense compared to

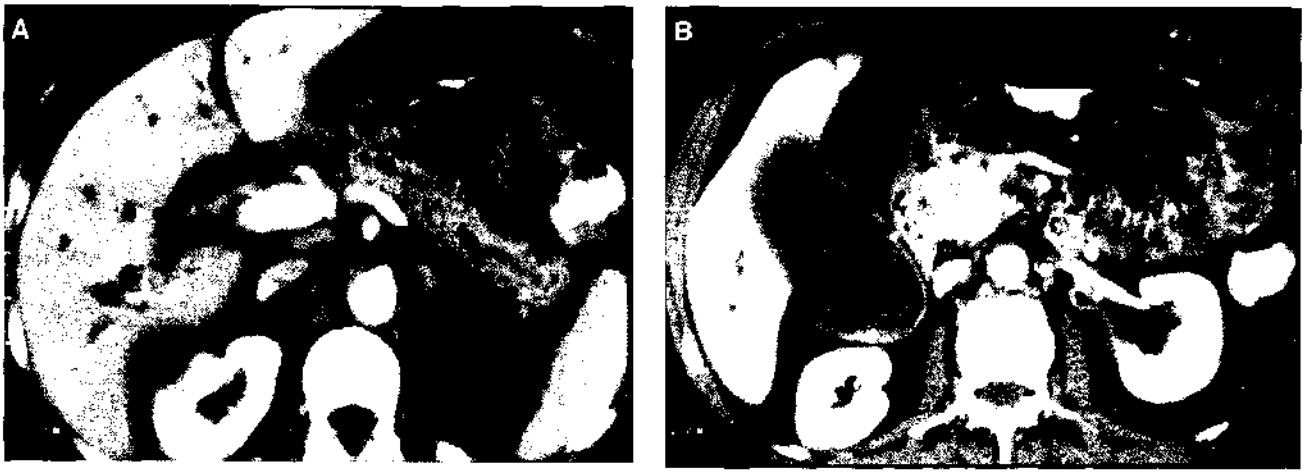


FIGURE 2 (A) CT scan showing both common bile duct and pancreatic duct dilation (double duct sign) in a patient with adenocarcinoma of the pancreatic head. (B) Note the massively enlarged, easily palpable gallbladder (Courvoisier's gallbladder).

normal pancreas). Dilation of the pancreatic duct proximal to the tumor is present in 70–80% of cases. Other common findings include pancreatic atrophy proximal to the tumor and a double duct sign if the tumor is located in the pancreatic head (Fig. 2).

The radiologic criteria for potentially resectable disease are defined as (1) the absence of extrapancreatic disease; (2) the absence of direct tumor extension to the superior mesenteric artery and celiac axis as defined by the presence of a fat plane between the low-density tumor and these arterial structures; and (3) a patent superior mesenteric–portal vein confluence (Fig. 3). In addition, CT is useful in determining the distant spread of pancreatic cancer. Liver metastases from pancreatic ductal carcinoma are hypovascular and are hypoattenuating to the liver on portal-phase scans (Fig. 3). Other common sites of metastases include the mesentery, the omentum, and the lungs. The presence of ascites usually indicates carcinomatosis and unresectability. False-negative CT scanning can be caused by small (less than 1 cm) metastasis to the liver and small peritoneal seedings.

## Magnetic Resonance Imaging

Although CT scan is typically the first choice in pancreatic imaging, MRI is rapidly evolving and may play an increasing role in the evaluation of the patient

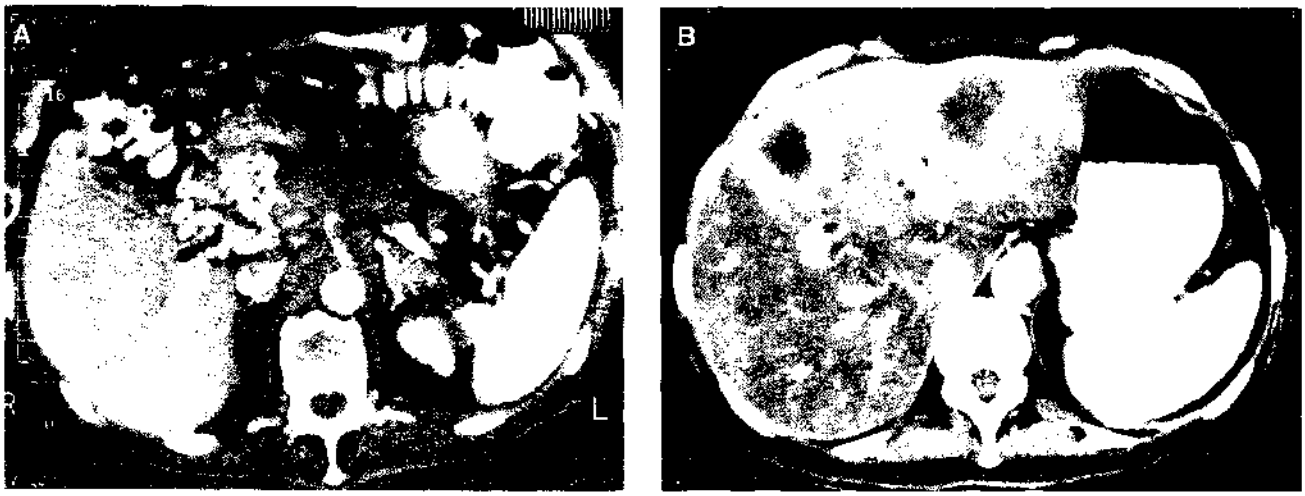


FIGURE 3 (A) CT scan of an unresectable adenocarcinoma of the pancreatic head with tumor encasement of the celiac artery. Note the extensive venous collateral secondary to occlusion of the superior mesenteric–portal vein confluence. (B) Large hypodense liver metastases in stage IV pancreatic adenocarcinoma.

with pancreatic cancer. Optimal MRI of the pancreas uses phased-array surface coils placed anteriorly on the patient's abdomen and posteriorly against the spine. Axial T1- and T2-weighted images are then obtained through the pancreas using a section thickness of 6 to 8 mm, with a 1 to 2 mm gap, respectively. On axial T1-weighted images, pancreatic abnormalities generally show decreased signal compared with the relatively high signal of the normal pancreas. Axial T2-weighted images are particularly useful in assessing the extent of inflammatory or cystic disease involving the pancreas. Duct dilation is demonstrated best on T2-weighted or magnetic resonance cholangiopancreatography (MRCP) images.

## Endoscopic Retrograde Cholangiopancreatography

Until recently, ERCP played a major role in the diagnosis of pancreatic cancer. However, rapid technologic advances in newer imaging modalities, such as MRCP and endoscopic ultrasonography, are redefining the indications for ERCP. Furthermore, ERCP is an invasive test that carries a morbidity of 2 to 3%, most commonly from pancreatitis and cholangitis. Therefore, the role of ERCP in the diagnosis of pancreatic cancer is rapidly diminishing.

The utility of preoperative endoscopic stent drainage in the jaundiced patient has been controversial. Recent data suggest that preoperative biliary drainage is associated with increased morbidity and mortality rates in patients undergoing pancreaticoduodenectomy. At the Memorial Sloan Kettering Cancer Center, over half of patients undergoing a Whipple resection underwent preoperative biliary drainage (endoscopic stents, percutaneous drains/stents, or surgical drainage). Preoperative biliary drainage was determined to be the only statistically significant variable associated with infectious complications, intra-abdominal abscess, and postoperative death. These investigators concluded that stent drainage should be avoided whenever possible in patients with potentially resectable pancreatic and peripancreatic lesions.

ERCP will continue to be indicated in the patient who is not a surgical candidate. Stent drainage is widely considered a reasonable way of palliating malignant obstructive jaundice in patients who are not candidates for operative palliation. Other indications for ERCP include biliary obstruction that is not associated with a pancreatic mass. In such cases, diagnostic ERCP may reveal a nonmalignant cause of biliary obstruction such as choledocholithiasis, which can be effectively treated by sphincterotomy and stone extraction. However, diagnostic endoscopic ultrasound is emerging as the initial evaluative method, reserving ERCP for sphincterotomy and stone extraction.

## Endoscopic Ultrasound

Endoscopic ultrasound produces high-frequency ultrasonographic images of the pancreas using the wall of the stomach and duodenum as an acoustical window. EUS provides an exceptional degree of anatomic detail that results in the ability to identify and stage lesions accurately. The pancreas, portal vein, celiac axis, common bile duct, gallbladder, and liver can all be visualized with EUS (Fig. 4). Although EUS itself does not provide a tissue diagnosis, the development of EUS-guided FNA makes diagnosis possible.

An abundance of data indicates that EUS is a sensitive method for the detection of pancreatic tumors. The larger series have demonstrated sensitivities of 90% or better. EUS is especially helpful for smaller lesions. In most studies, EUS is superior to transabdominal ultrasound and CT and is equivalent to ERCP for lesions that are 3 cm or smaller. Most tumors are relatively hypoechoic compared with pancreatic parenchyma, although the echo pattern becomes mixed and more variable the larger the size of the tumor. Cancers tend to have an irregular margin, sometimes with extending pseudopodia, but malignant lesions smaller than 3 cm may have a smooth margin. Unfortunately, areas of focal inflammation can also have a similar hypoechoic pattern and therefore the specificity for EUS for

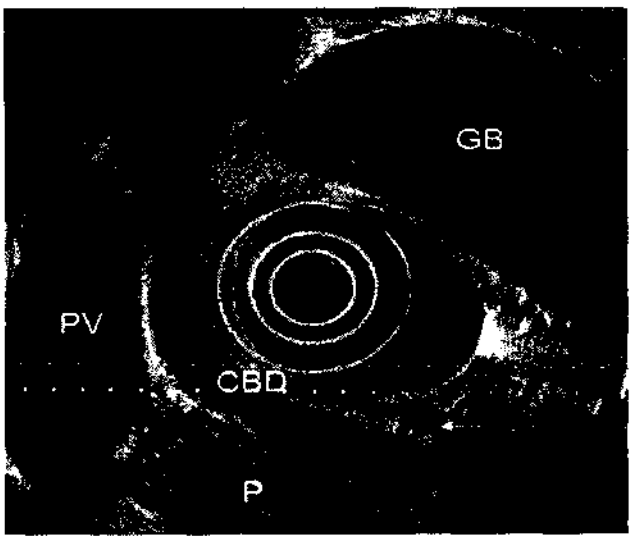


FIGURE 4 Endoscopic ultrasound of the pancreas. CBD, common bile duct; GB, gallbladder; P, pancreas; PV, portal vein.

differentiating pancreatic cancer from focal pancreatitis is approximately 70%.

### Fine-Needle Aspiration Cytology

In patients with potentially resectable disease, percutaneous or endoscopic ultrasound-guided needle biopsy should be considered *only* in cases where pretreatment cytologic confirmation of the diagnosis is important, such as in patients being considered for preoperative multimodality therapy as part of a clinical trial. FNA is performed by passing a 21- to 23-gauge needle into the pancreatic mass using the appropriate imaging technique for guidance and then applying suction with a syringe. The specimen is then expressed onto a microscope slide, smeared, fixed in 95% alcohol, and stained by the Papanicolaou or other method. If an experienced cytopathologist is available, a diagnosis can generally be made within 20 minutes of obtaining the biopsy.

The typical findings of pancreatic adenocarcinoma include single or irregularly arranged clusters of cells exhibiting cellular pleomorphism, large vesicular nuclei, and prominent nucleoli. However, such cytologic appearances may sometimes fail to differentiate between an adenocarcinoma, a lymphoma, or an islet cell tumor. The main problem with fine-needle aspiration, however, is sampling error. A negative cytologic specimen does *not* exclude cancer.

FNA of the pancreas is useful for masses in the body and tail of the gland because cancers in this location are usually unresectable, especially if there is CT or EUS evidence of unresectability. It is especially valuable in the frail or elderly patient in whom one wishes to avoid a purely diagnostic laparotomy when surgical palliation is not indicated or warranted. The technique, however, should not be used for small, potentially resectable cancers because of sampling error and the theoretical possibility of seeding along the needle tract. The pancreas is a vascular organ with a rich lymphatic network. Common sense dictates that meddlesome needling can disseminate a cancer that already has a high propensity for local invasion and vascular permeation. When FNA is indicated, EUS may be the preferred approach, owing to a more direct route that does not violate the peritoneum.

### Laparoscopy

Pancreatic cancer is notorious for its high predilection for liver and peritoneal metastases. Identifying small (1 to 2 mm) implants that are not definable on CT scan can now be achieved with laparoscopy. Laparoscopy is minimally invasive and can establish the diagnosis through visualization and biopsy of metastatic lesions. It can also serve as an avenue for obtaining peritoneal cytology, which can be positive in 20 to 30% of cases. With peritoneal lavage, cytologic exam of washings can be positive up to 30% of the time, indicating tumor unresectability and poor survival (median $<6$ months).

The exact role of laparoscopy as a diagnostic tool and in the staging of pancreatic cancer remains to be defined. Studies by Cuschieri and Warshaw have established the value of laparoscopy in detecting liver and peritoneal metastases. However, many of their patients had locally advanced disease that was not amenable to surgical resection. When laparoscopy is limited to patients who fulfilled strict CT criteria for resectability, Fuhrman and colleagues could not confirm the diagnostic value of routine preoperative laparoscopic evaluation.

### Sequence of Diagnostic Tests

The goal of preoperative diagnostic staging in pancreatic cancer is to differentiate the small group of patients who have a potentially resectable localized cancer from those with locally advanced disease and/or disseminated metastases. Figure 5 is an algorithm for the diagnosis and staging of pancreatic tumors. Patients with a clinical suspicion of pancreatic cancer should undergo physical examination and laboratory evaluation including CA 19-9 levels. Helical CT scan is the initial modality used to image the pancreas. MRI offers an alternative or adjunct to CT imaging of the pancreas. If the CT scan is equivocal, endoscopic ultrasound has been found to be useful, especially in the detection of small ampullary or periampullary neoplasms. If EUS reveals findings of unresectablity, such as superior mesenteric or celiac artery encasement, portal vein occlusion, or liver metastases, a tissue diagnosis can be established in the same session by EUS-guided FNA.

If the patient appears to have localized, surgically resectable disease by CT and EUS, it is appropriate to prepare the patient for an operation. Laparoscopy may be used as a preliminary test to detect small peritoneal or liver metastases that were not seen on initial imaging studies. The authors do not advocate routine biopsy of the mass or peripancreatic lymph nodes at surgery because these are excised *en bloc* with the specimen. On the other hand, if the tumor is found to be unresectable at operation, every attempt must be made to establish a tissue diagnosis by biopsy and frozen section histology prior to leaving the operating room. This removes any doubt about the exact diagnosis and the patient can be referred for palliative treatment.

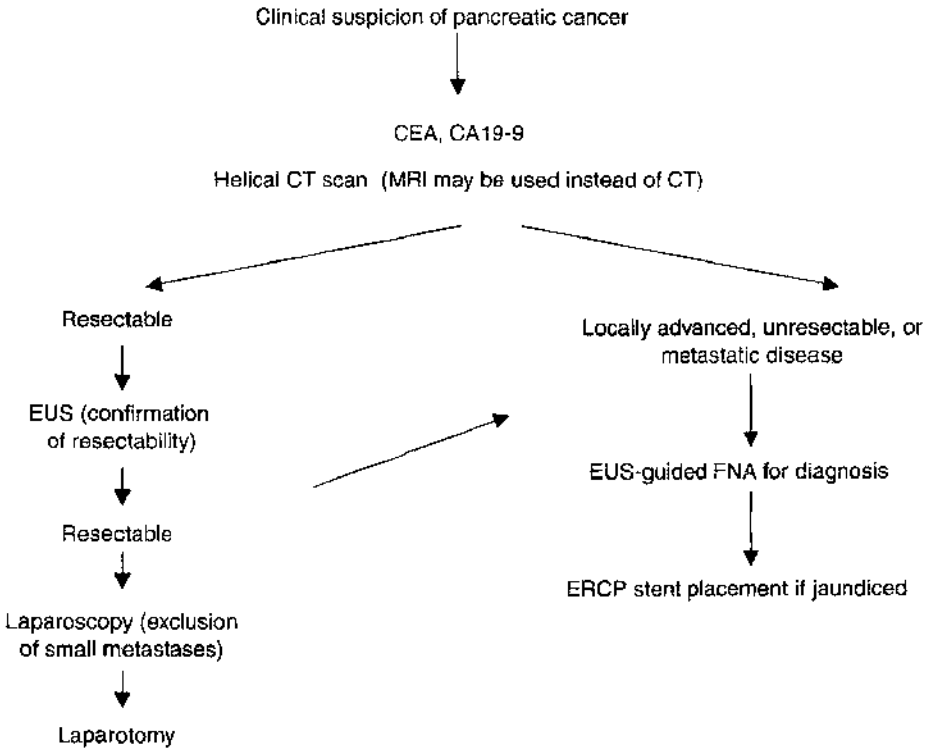


FIGURE 5 Algorithm for diagnosis and staging of pancreatic tumors.

## CURRENT TREATMENT STRATEGIES AND PROGNOSIS

Emphasis must be placed on preoperative evaluation and adequate preparation of patient with pancreatic cancer. As mentioned earlier, CT scan, cytology, and EUS provide the surgeon with valuable preoperative information and obviate the need for time-consuming maneuvers on the operating table. It cannot be overemphasized that pancreatic exploration with a view to resection should not be performed by the occasional surgeon or resident in training or at institutions where there is not sufficient back-up expertise (endoscopy, radiology, cytology, and critical care) that is necessary for the care and management of these difficult problems.

### Surgery

Pancreaticoduodenectomy (Whipple operation) is most commonly employed for tumors of the head of the pancreas (Fig. 6). The operation is optimal for malignant tumors that are confined to the duodenum, ampulla of Vater, or lower common bile duct. The neck of the gland is divided to the left of the superior mesenteric vein and the body and tail of the pancreas and spleen are left undisturbed. *En bloc* excision of the regional lymph nodes from the porta hepatis, aortocaval, and superior mesenteric regions again forms part of the operation. With the Whipple operation, endocrine function can be preserved. Although there is the possibility of an anastomotic leak from the pancreaticojejunostomy, this complication occurs in less than 10–15% of patients at centers experienced with pancreatic surgery. Also, more effective management of pancreatic anastomotic leakage with hyperalimentation, percutaneous drainage, and a somatostatin analogue has reduced the magnitude of this problem. Total pancreatectomy should be reserved for situations when there is tumor at the pancreatic margin on serial frozen sections or if the pancreas is not suitable for an anastomosis. A pylorus-preserving Whipple operation is a reasonable alternative but may result in transient gastric stasis.

A cancer of the pancreas is considered unresectable if there are distant (liver or peritoneal) metastases, invasion of major vessels (portal vein, hepatic artery, superior mesenteric vessels, or celiac axis), or any extension beyond the area of usual total pancreatectomy specimen. The possible exception is the case of isolated portal vein invasion provided the vein is patent. In these selected cases, portal vein resection with interposition graft placement has been described. Puckering of the

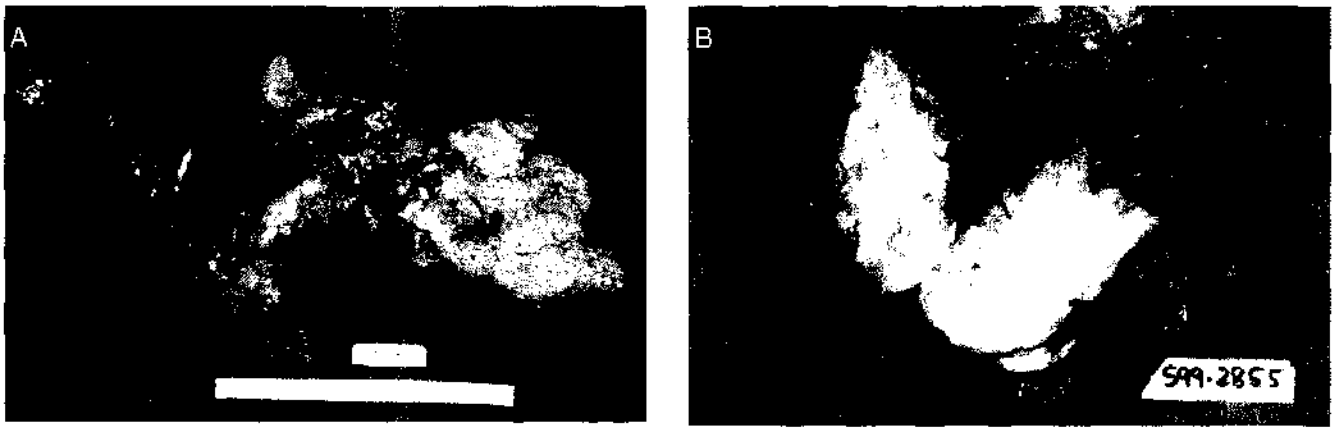


FIGURE 6 (A) Whipple specimen from a patient with pancreatic cancer. (B) The tumor is sectioned.

transverse mesocolon per se does not always indicate unresectability since the transverse mesocolon and, if necessary, the transverse colon can be excised in a total pancreatectomy specimen if there are no contraindications to a resection.

The mortality for major pancreatic resection is between 0 and 5% at specialized centers. Death as a result of operative complications usually occurs within the first 2 months of operation. After 2 months and up to 2 years later, death is usually due to metastatic pancreatic cancer although a few individuals can present as late as the end of the third year with metastatic disease. If the patient has survived 3 years, the cause of death is usually unrelated to pancreatic cancer. The estimated 5-year survival rate in patients with localized adenocarcinoma of the pancreas who undergo surgical resection of the primary tumor ranges from 6 to 24%. Survival after potentially curative resection for periampullary neoplasms including pancreatic cancer depends primarily on pathologic factors. Factors shown to influence survival include tumor size, lymph node metastases, tumor differentiation, margin status, and vascular and perineural invasion. In addition, tumors of the ampulla of Vater, distal common bile duct, and duodenum have a more favorable prognosis than that of pancreatic ductal carcinoma.

### Chemotherapy and Radiation

Data from several randomized trials have shown a significant survival benefit in patients treated with infusional 5-fluorouracil (5-FU) and external beam radiation following pancreatectomy. Therefore, in patients who are well enough to tolerate it, adjuvant chemoradiation is recommended. Newer agents, such as gemcitabine, are currently being studied in combination with radiation as alternatives to 5-FU.

If diagnostic studies indicate that the patient has locally advanced, unresectable disease or metastatic disease, nonoperative palliation of jaundice can usually be achieved by endoscopically placed biliary stents. If the patient survives for more than a few months, recurrent cholangitis associated with stent blockage is a problem that necessitates regular endoscopic removal and replacement of the stent. Newer self-expandible metallic devices, such as the Wall stent, may provide improved patency rates compared to plastic stents. Percutaneous transhepatic placement of an internal expandable metal stent is being tried by interventional radiologists and offers yet another option for palliation of the jaundiced patient with malignant biliary obstruction.

If these nonoperative techniques are unsuccessful, biliary tract decompression can be performed either by cholecystojejunostomy or by hepaticojejunostomy (each with a diverting enterostomy), depending on whether the cystic duct is widely patent and is in full communication with the biliary tree proximal to obstructing cancer. When there is evidence of gastric outlet obstruction from tumor compression of the duodenum, gastrojejunostomy can be performed. Chemoradiation with 5-FU and external beam irradiation for locally advanced, unresectable tumors is indicated. If liver metastasis or carcinomatosis is found at laparotomy, single-agent chemotherapy with gemcitabine may provide palliation and improve the patient's quality of life.

## CONCLUSION

Pancreatic cancer is a common cause of cancer-related mortality. Although the exact etiology for pancreatic cancer is unknown, the molecular events that take place involve mutations in oncogenes and tumor

suppressor genes. The diagnosis of pancreatic cancer continues to evolve with new technological advances in imaging, endoscopy, and biochemical tumor markers. The goal of such new diagnostic testing remains earlier tumor detection, thus providing the patient with the best chance for cure. The primary treatment for localized disease is surgical resection. Adjuvant chemoradiation has been shown by most, but not all, studies to improve local control and survival. In patients with advanced disease, palliation of jaundice, pain, and gastric outlet obstruction can be achieved by the use of stents and/or surgical bypass. Newer agents, such as gemcitabine, have been shown to improve the quality of life for patients with advanced pancreatic cancer.

## See Also the Following Articles

**Cancer, Overview • Computed Tomography (CT) • Endoscopic Ultrasonography • Laparoscopy • Magnetic Resonance Imaging (MRI) • Pancreatic Cancer • Pancreatic Tumors, Other**

## Further Reading


Bluemke, D. A., and Fishman, E. K. (1998). CT and MR evaluation of pancreatic cancer. *Surg. Oncol. Clin. North Am.* 7, 103–124.

Bouvet, M., Binmoeller, K. F., and Moossa, A. R. (2001). The diagnosis of adenocarcinoma of the pancreas. *In* "Atlas of Clinical Oncology: Pancreatic Cancer" (J. L. Cameron, ed.), pp. 67–85. B. C. Decker, Hamilton, Ontario, Canada.

Bouvet, M., Gamagami, R. A., Gilpin, E. A., Romeo, O., Sasson, A., Easter, D. W., and Moossa, A. R. (2000). Factors influencing survival after resection for periampullary neoplasms. *Am. J. Surg.* **180**, 13–17.

Casey, G., Yamanaka, Y., Friess, H., Kobrin, M., Lopez, M., Buchler, M., Beger, H., and Korc, M. (1993). p53 mutations are common in pancreatic cancer and are absent in chronic pancreatitis. *Cancer Lett.* 69, 151–160.

Cerny, W. L., Mangold, K. A., and Scarpelli, D. G. (1992). K-ras mutation is an early event in pancreatic duct carcinogenesis in the Syrian golden hamster. *Cancer Res.* 52, 4507–4513.

Cuschieri, A. (1988). Laparoscopy for pancreatic cancer—Does it benefit the patient? *Eur. J. Surg. Oncol.* **14**, 41–44.

Evans, D. B., Abbruzzese, J. L., and Rich, T. A. (1997). Cancer of the pancreas. *In* "Cancer Principles and Practice of Oncology" (V. T. DeVita, S. Hellman, and S. A. Rosenberg, eds.), pp. 1054–1081. Lippincott–Raven Press, Philadelphia, PA.

Fernandez-del Castillo, C., Rattner, D. W., and Warshaw, A. L. (1995). Further experience with laparoscopy and peritoneal cytology in the staging of pancreatic cancer. *Br. J. Surg.* 82, 1127–1129.

Fuhrman, G. M., Charnsangavej, C., Abbruzzese, J. L., Cleary, K. R., Martin, R. G., Fenoglio, C. J., and Evans, D. B. (1994). Thin-section contrast-enhanced computed tomography accurately predicts the resectability of malignant pancreatic neoplasms. *Am. J. Surg.* **167**, 104–111, discussion **111**–113.

Hahn, S. A., Schutte, M., Hoque, A. T., Moskaluk, C. A., da Costa, L. T., Rozenblum, E., Weinstein, C. L., Fischer, A., Yeo, C. J., Hruban, R. H., and Kern, S. E. (1996). DPC4, a candidate tumor suppressor gene at human chromosome 18q21.1. *Science* 271, 350–353.

Moossa, A. R., and Gamagami, R. A. (1995). Diagnosis and staging of pancreatic neoplasms. *Surg. Clin. North Am.* 75, 871–890.

Povoski, S. P., Karpeh, M. S., Jr., Conlon, K. C., Blumgart, L. H., and Brennan, M. F. (1999). Association of preoperative biliary drainage with postoperative outcome following pancreaticoduodenectomy [see comments]. *Ann. Surg.* **230**, 131–142.

Safi, F., Schlosser, W., Falkenreck, S., and Beger, H. G. (1998). Prognostic value of CA 19–9 serum course in pancreatic cancer. *Hepatogastroenterology* 45, 253–259.

Spitz, F. R., Abbruzzese, J. L., Lee, J. E., Pisters, P. W., Lowy, A. M., Fenoglio, C. J., Cleary, K. R., Janjan, N. A., Goswitz, M. S., Rich, T. A., and Evans, D. B. (1997). Preoperative and postoperative chemoradiation strategies in patients treated with pancreaticoduodenectomy for adenocarcinoma of the pancreas [see comments]. *J. Clin. Oncol.* 15, 928–937.

Yeo, C. J., Cameron, J. L., Sohn, T. A., Lillemoe, K. D., Pitt, H. A., Talamini, M. A., Hruban, R. H., Ord, S. E., Sauter, P. K., Coleman, J., Zahurak, M. L., Grochow, L. B., and Abrams, R. A. (1997). Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: Pathology, complications, and outcomes. *Ann. Surg.* 226, 248–257; discussion 257–260.

# Pancreatic Enzyme Secretion (Physiology)

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**acetylcholine** The major neurotransmitter of the parasympathetic nervous system.
**cholecystokinin** A gastrointestinal peptide hormone with multiple functions regulating pancreatic secretion and gastrointestinal function.
**cholecystokinin-releasing peptide** A trypsin-sensitive peptide whose presence in the lumen of the intestine leads to the release of cholecystokinin from intestinal enteroendocrine cells.
**chyme** The mixture of ingested foodstuffs with gastric secretions.
**dorsal motor nucleus of the vagus** A region of the brainstem that contains nuclei for vagal efferent neurons.
**enteroendocrine cells** Endocrine cells found throughout the epithelium of the gastrointestinal tract.
**G-proteins** Guanine nucleotide-binding proteins.
**protein kinases** Enzymes that add phosphate groups to proteins and thereby regulate their functions.
**secretin** A gastrointestinal peptide hormone that stimulates bicarbonate and fluid secretion from pancreatic ducts.
**vagus nerve** The 10th cranial nerve, which innervates much of the digestive system, including the pancreas.
**zymogen granule** The membrane-bound granules within pancreatic acinar cells that store digestive enzymes.

**Pancreatic secretion occurs in various "phases" corresponding to the demand for pancreatic juice. The major phases are the (1) interdigestive, (2) cephalic, (3) gastric, (4) intestinal, and (5) humoral phases. The interdigestive phase is that period between meals when there is little need for pancreatic juice. The cephalic phase occurs when there is anticipation of food, perhaps due to smell, taste, or habitual behavior associated with feeding. The gastric phase begins with the ingestion of food and corresponds to that period of time when the food resides within the stomach, before entering the small intestine. The intestinal phase is the time during which the food resides within the intestine; this phase corresponds to the period when there is peak demand for pancreatic juice. The humoral phase describes the time after significant digestion has taken place and nutrient absorption has occurred, but while active digestive processes are still present. Specific regulatory mechanisms are responsible for regulating pancreatic secretion during these different phases and these regulatory mechanisms are the primary focus of this article.**

## INTRODUCTION

The exocrine pancreas produces a bicarbonate-rich secretion termed "pancreatic juice" that contains abundant digestive enzymes, proteins specialized for the molecular disassembly of complex organic constituents. Pancreatic juice is necessary for the proper digestion of ingested foodstuffs. Relative to its weight, the pancreas secretes more protein than any other organ. Without proper digestion, food cannot be absorbed and hence insufficient pancreatic secretion can lead to malnutrition. Furthermore, undigested food that reaches the colon promotes bloating, gas, and diarrhea. Thus, it is important that pancreatic secretion matches food intake.

Pancreatic juice originates from the exocrine pancreas, which is composed of numerous acini, cluster-like groups of acinar cells, and associated ducts. The acinar cells are responsible for the synthesis, storage within zymogen granules, and regulated release of the digestive enzymes and may also contribute to the fluid component of pancreatic juice. The duct cells provide a conduit for passage of pancreatic juice out of the pancreas and are also the primary site of pancreatic bicarbonate and fluid secretion. Because the major constituents of pancreatic juice, digestive enzymes and bicarbonate-rich fluid, originate in two different cell types, it is possible experimentally to separate the factors that influence each component. However, physiologically these components are not separated but occur in a coordinated manner with greater or lesser proportions of each being secreted depending on the demand. In addition to these two basic cell types that produce pancreatic juice, there are other important influences on pancreatic secretion. One such influence is the sphincter of Oddi. This sphincter, located at the entrance of the common bile/pancreatic duct into the intestine, regulates the flow of juice from the pancreas into the intestine and is influenced by nervous and hormonal inputs. Another influence on pancreatic secretion is pancreatic blood flow. Secretion is an energy-consuming process such that increased blood flow, supplying oxygen to the tissue, is required during

 

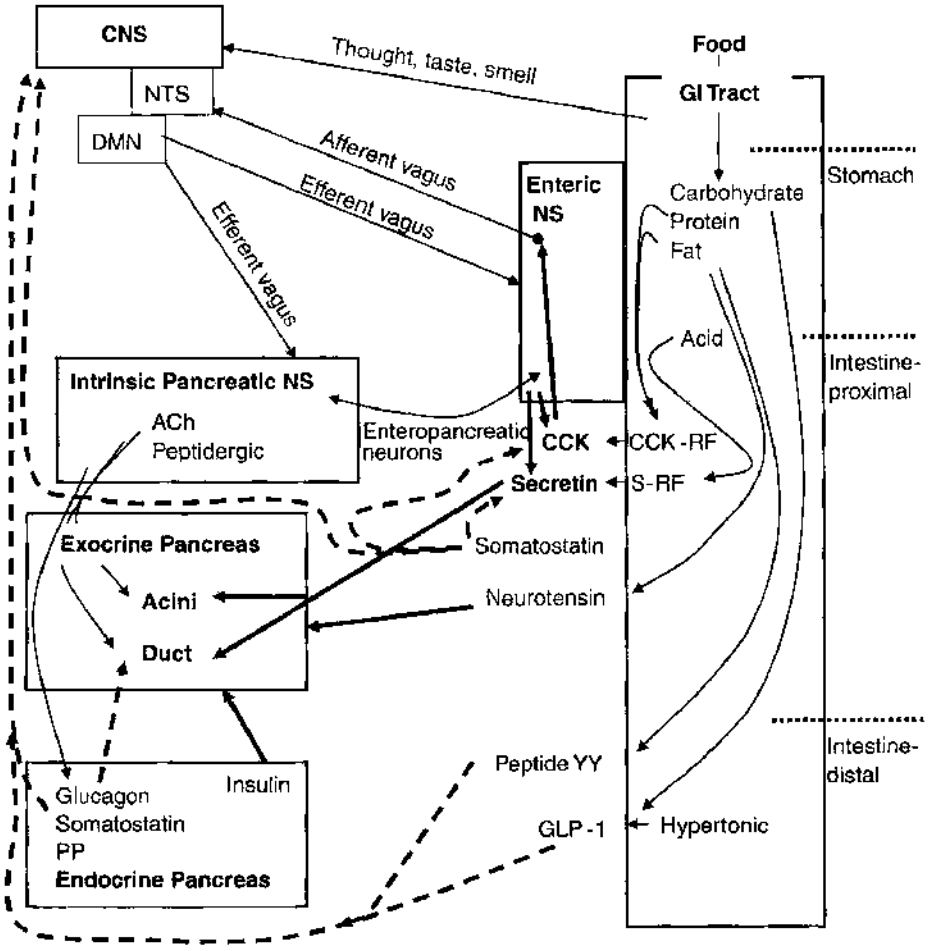


FIGURE 1 Regulation of exocrine pancreatic secretion. Pancreatic secretion of protein from acinar cells and of fluid and bicarbonate from duct cells is regulated by cholinergic (ACh) and peptidergic neurons within the intrinsic pancreatic neural network. Activity of the intrapancreatic nerves is modulated by extrinsic innervation through the vagus nerve originating in the brainstem. Vagal signals are influenced by information arising from sensory input both within the vagus and from other central nervous system (CNS) centers that are coordinated in the nucleus of the solitary tract (NTS). Pancreatic secretion is also modulated both positively (solid arrows) and negatively (dashed arrows) by hormones. Hormones arise both from the endocrine pancreas and from enteroendocrine cells within the epithelium of the intestine. Hormones can have direct effects or influence the nervous system. CCK and secretin are the major hormonal regulators of pancreatic secretion. CCK influences pancreatic secretion in humans by activating afferent neurons within the enteric nervous system. Secretin acts directly on pancreatic duct cells and synergizes with the effects of ACh on acinar cells. Somatostatin is an inhibitory substance that appears to act as a hormone on the CNS and also as a paracrine inhibitor of CCK and secretin release. Hormone-secreting cells and nerves within the gastrointestinal (GI) tract respond to the presence of specific components of chyme within specific compartments of the GI tract. The release of CCK and secretin appears to be regulated by releasing factors originating from cells within the GI tract. Signals from proximal portions of the GI tract tend to be stimulatory, whereas those from distal portions tend to be inhibitory.

active secretion and factors that diminish pancreatic blood flow reduce pancreatic secretion.

## GENERAL ISSUES CONCERNING THE INTEGRATIVE PHYSIOLOGIC REGULATION OF PANCREATIC ENZYME SECRETION

Pancreatic secretion is influenced by many types of regulators, including hormones, neurotransmitters, and paracrine effectors. Figure 1 summarizes the roles of several of the major regulatory factors that will be discussed in this article. As noted in Fig. 1, the effects of regulatory substances on pancreatic secretion can occur either directly, by effects on acinar or duct cells, or indirectly, by effects on afferent neurons, the central nervous system (CNS), or enteroendocrine cells. Regulatory substances can also have interactions with one another that can be antagonistic, additive, or synergistic.

Many factors are able to influence pancreatic secretion experimentally. However, not all factors that are able to affect secretion do so in a normal physiological setting. Thus, it becomes important to distinguish between those that normally regulate pancreatic secretion, generally termed "physiological," and those that influence secretion only under experimental conditions, often termed "pharmacological." In order for a regulatory substance to be considered physiological, it must meet certain criteria. First, the concentration of the substance must increase in the physiologically relevant compartment during the appropriate phase of digestion. For a hormone, that means that plasma levels, which are relatively easy to monitor, must be elevated. For neurotransmitters or paracrine regulators, the relevant compartment is much less accessible and determination of relevant concentrations can be difficult. Second, concentrations of the candidate regulator that occur naturally must be able to influence pancreatic secretion. Again, many substances can affect pancreatic secretion at high concentrations that do not influence pancreatic secretion in normal circumstances. This criterion requires knowledge of the physiologic concentration, which is again easier for hormones than for neurotransmitters or paracrine substances. Furthermore, some regulators have important synergistic interactions with other regulators. In this case, administration of one without the other may not be sufficient to elicit a response. The third criterion is that inhibition of the regulator should influence pancreatic secretion during a normal meal. Experimental strategies to test this may include pharmacological, immunological, and genetic approaches. Each of these experimental approaches has its caveats. However, when several approaches verify the same role, then strong conclusions can be made. Similarly, it may not be possible to fulfill all three of these criteria for a specific molecule, but the more criteria that can be fulfilled, the stronger the argument for a physiologic role.

## INTEGRATIVE REGULATORS OF PANCREATIC SECRETION

### Neural Mechanisms

#### *Intrinsic Pancreatic Neurons and the Enteropancreatic Neural Reflex*

Intrapancreatic postganglionic cholinergic and noncholinergic neurons directly influence acinar and duct cell secretory activity. These neurons are activated by the central nervous system via the vagus nerve. Important vagovagal reflexes occur during gastric and intestinal phases of pancreatic secretion in which both afferent and efferent nerves are carried by the vagus. The vagal afferent nerve terminals in the stomach and duodenum are responsive to cholecystokinin (CCK), leptin, serotonin, interleukin-1B, and mechanical stimuli and communicate with the central nervous system. Direct neural connections have also been recently described between neurons in ganglia of the myenteric plexi of the stomach and duodenum and the intrapancreatic plexus. These enteropancreatic neural pathways have cholinergic and serotonergic components.

#### *The Central Nervous System Controls Pancreatic Secretion through the Autonomic Nervous System*

During the cephalic phase of pancreatic secretion, information from olfactory, visual and other inputs is integrated at the level of the nucleus of the solitary tract (NTS), which is located in the medulla or brainstem. Similarly, during later phases of pancreatic secretion, information arriving from vagal afferent neurons is processed in the NTS. The NTS projects to the efferent vagal neurons in the dorsal motor nucleus of the vagus. Central stimulants of vagally mediated pancreatic secretion remain to be clearly identified. However, central administration of orexin-A and thyrotropin-releasing hormone stimulates pancreatic juice flow. Central inhibitors of vagal efferent neurons include pancreastatin and pancreatic polypeptide.

The parasympathetic nervous system is the major controller of pancreatic secretion, with the vagus nerve being the primary source of parasympathetic

innervation. Activation of parasympathetic activity stimulates pancreatic fluid and enzyme secretion. In contrast, the sympathetic nervous system primarily plays an inhibitory role in regulating pancreatic secretion. Sympathetic innervation occurs chiefly through the splanchnic nerves. Splanchnic neural activation appears to inhibit pancreatic secretion largely through its vasoconstrictive effects on pancreatic blood flow.

### *Neurotransmitters Regulating Pancreatic Secretion*

The most important stimulant of pancreatic secretion is acetylcholine released from the nerve termini of intrapancreatic neurons, which acts directly on both acinar and duct cells through the occupation of muscarinic cholinergic receptors (m3 receptors). Activation of these receptors leads to increased cellular signaling events, which result in the exocytotic release of digestive enzymes from the pancreatic acinar cell and increased bicarbonate and fluid secretion from the duct cells. Thus, inhibition of cholinergic nervous transmission, for example, by administration of atropine, inhibits both fluid and enzyme secretion.

There are also direct actions of noncholinergic, peptidergic neurotransmitters released from intrapancreatic neurons. Gastrin-releasing peptide, vasoactive intestinal peptide (VIP), and pituitary adenylate cyclase-activating polypeptide are stored in and released from intrapancreatic neurons and can act as stimulants of pancreatic secretion. These effects are more pronounced in certain animal species. Somatostatin, peptide tyrosine tyrosylamide (PYY), and enkephalins are examples of peptides that act as inhibitors of pancreatic secretion. Few of these, however, act directly on acinar cells and most inhibit the CNS or act at the level of intrapancreatic ganglia. The specific roles of these peptidergic neurotransmitters has been difficult to determine because of significant interactions between regulators and species differences in the activity of the regulators.

## Hormonal Mechanisms

Pancreatic secretion is also regulated by the actions of a number of gastrointestinal hormones that originate from endocrine cells within the mucosa of the gastrointestinal tract and are therefore referred to as "enteroendocrine" cells. These hormones are released into the blood on ingestion of a meal. Individual hormones are regulated by specific components of the chyme, including both ingested foodstuffs and components secreted into the gut by mucosal cells and accessory organs. Hormones travel through the blood and can have direct effects on pancreatic acinar or duct cells via high-affinity receptors for the hormones or they may interact with afferent neurons to regulate local neural mechanisms or act on central neural sites.

### *Cholecystokinin*

CCK is the major peptide hormone that regulates pancreatic protein secretion. CCK also influences the flow of secretions into the small intestine by relaxing the sphincter of Oddi and contracting the gallbladder. In addition, CCK reduces gastric emptying. Taken together, these actions of CCK regulate the movement of both food and digestive secretions into the small intestine. CCK also supports pancreatic secretion through its tropic effects on the pancreas. It stimulates the synthesis of new digestive enzymes and maintains the growth of the pancreas. In various species, the pancreas atrophies in the absence of intralumenal nutrients and will grow under conditions in which plasma CCK is chronically elevated, as occurs following administration of trypsin inhibitor.

CCK is produced and secreted by a specific class of intestinal enteroendocrine cells (I cells). It is released by hydrolytic products of digestion including amino acids and fatty acids. The mechanism by which these nutrients induce CCK release is not fully understood. The presence of active trypsin in the intestinal lumen inhibits CCK release in many species and ingestion of trypsin inhibitors causes high and sustained levels of plasma CCK. Diversion of the pancreatic juice from the duodenum also increases CCK plasma levels. Taken together, these observations suggest that feedback inhibition of CCK release occurs. The "feedback hypothesis" suggests that proteins bind or inhibit intralumenal endopeptidases, which would otherwise inactivate a CCK-releasing peptide. Several candidate molecules that have the ability to increase CCK release when infused into the small intestine have been identified. However, the physiological significance of these CCK-releasing peptides remains to be elucidated.

CCK plays a central role in the stimulation of pancreatic secretion during a meal. Under fasting conditions, the plasma CCK levels are very low (~1 pmol/liter in humans). After ingestion of a typical meal, the concentration increases to 6–8 pmol/liter within 10 to 30 min, followed by a gradual decline to basal levels over ~3 h. Infusion of similar doses of CCK produces the same levels of pancreatic enzyme secretion. Furthermore, administration of CCK antagonists produces a 50–60% reduction of meal-stimulated pancreatic secretion.

The mechanism of CCK stimulation of pancreatic secretion appears to be somewhat determined by the species. In rodents, receptors exist on pancreatic acinar cells that can respond directly to CCK within physiologic concentrations. However, in humans, these receptors are not expressed on pancreatic acinar cells. Therefore, it appears that the major mechanism of CCK stimulation of pancreatic secretion is via an indirect mechanism that involves activation of receptors on vagal afferent neurons that are present within the enteric nervous plexus in the intestinal mucosa. These neurons communicate with the central nervous system and a stimulatory signal is conveyed back to the pancreas via vagal efferents to mediate secretion that is dependent on cholinergic signaling. The major evidence in support of this model is that the cholinergic antagonist atropine blocks pancreatic secretion in response to infusion of physiological doses of CCK. There may also be effects of CCK on enteropancreatic neurons that do not require an intact vagus nerve, as CCK can stimulate pancreatic secretion in patients after vagotomy. However, this remains unproven.

### *Secretin*

Secretin is the intestinal peptide hormone that is the major regulator of pancreatic fluid and bicarbonate secretion. Secretin is released from intestinal enteroendocrine cells (S cells) in response to a reduction in duodenal pH. Acidic chyme entering from the stomach leads to secretin release and subsequent pancreatic bicarbonate secretion, which neutralizes gastric acid. The mechanisms responsible for secretin release remain under active investigation, but there is some evidence for a secretin-releasing factor that may be released by low-pH conditions. Nonacid factors may also play a role in secretin release. Bile, as well as fatty acids and other digestive products of fat, can increase plasma secretin levels. However, the physiologic importance of these nonacid factors is questionable, as plasma secretin does not increase in subjects in whom meal-induced acid secretion is neutralized.

Infusion of secretin at concentrations similar to those observed after a meal leads to the stimulation of pancreatic fluid and bicarbonate secretion, and neutralization of secretin, using antiserum, greatly reduces pancreatic bicarbonate release. Secretin activates specific receptors expressed on pancreatic duct and acinar cells. Thus, secretin appears to directly mediate its effects on pancreatic secretion. Secretin appears to act in synergy with CCK, as the combination of these hormones leads to much greater levels of pancreatic secretion than either one alone.

### *Other Stimulatory Hormones*

A variety of other hormones have been reported to have stimulatory effects on pancreatic secretion. Insulin potentiates the secretory response to CCK and secretin, an observation that may explain why enzyme secretion is frequently reduced in human diabetics who otherwise do not exhibit overt pancreatic disease. The influences of insulin on exocrine secretion may also help to explain the location of the insulin-secreting cells that are within the islets of Langerhans, which are dispersed throughout the exocrine pancreas. Insulin is also critical for maintaining rates of acinar cell protein synthesis and adequate stores of digestive enzymes.

Other hormones that may be stimulatory for pancreatic secretion include gastrin, neurotensin, and motilin. Gastrin, which is structurally related to CCK, can also stimulate pancreatic secretion when infused at relatively high concentrations. However, it is unclear whether or not the serum levels of gastrin obtained after a meal are sufficient for pancreatic stimulation. Neurotensin is released from enteroendocrine cells by intestinal fatty acids and infusion of neurotensin can stimulate pancreatic secretion. However, the concentrations of neurotensin required to stimulate pancreatic secretion are higher than those normally observed after a meal. Therefore, it is unclear whether or not neurotensin is a physiological stimulant of pancreatic secretion. Motilin is a hormone that is known to regulate the cyclic interdigestive migrating motor complex that influences intestinal motility. Bolus injection of motilin also results in a transient increase in pancreatic secretion. Thus, it has been suggested that motilin may regulate the cyclic secretion of pancreatic juice during the interdigestive state.

### *Inhibitory Hormones*

After a meal, pancreatic secretory levels decline and return to a low basal level. Much of this reduction in pancreatic secretion is due to a decrease in the levels of stimulatory signals. However, there is also evidence for inhibitory control. For example, infusion of glucose or amino acids to raise serum concentrations inhibits pancreatic secretory responses to a test meal. The release of inhibitory hormones from the islets of Langerhans, distal small intestine, and colon has been postulated to account for this observation. The most well-established inhibitory hormones include glucagon and its related peptides, as well as somatostatin, and PYY.

Glucagon and the glucagon-related molecules oxyntomodulin and glucagon-like peptide-1 (GLP-1) inhibit pancreatic secretion stimulated by secretin and CCK or by ingestion of a test meal. The inhibitory effect

includes a reduction of fluid and bicarbonate as well as enzyme secretion. Glucagon is released from pancreatic islets of Langerhans by the hyperaminoacidemia observed after a high-protein meal. Oxyntomodulin is a 37-amino-acid glucagon-containing peptide that is 10 times more potent than pancreatic glucagon in terms of its ability to reduce pancreatic secretion. Oxyntomodulin originates in enteroendocrine cells located in the distal intestine and its release is stimulated by hypertonic solutions. GLP-1 is another GI hormone derived from the glucagon precursor whose cells of origin (K cells) are located within the epithelium of the more distal small intestine. GLP-1 appears to be secreted in response to carbohydrates within the gut lumen. Glucagon, oxyntomodulin, and GLP-1 appear to inhibit pancreatic secretion via action on a central vagal site.

Somatostatin is another candidate as a physiological inhibitor of pancreatic secretion. Somatostatin is produced and secreted by both delta cells of the islets of Langerhans and enteric endocrine cells. Infusion of somatostatin inhibits CCK-stimulated pancreatic enzyme secretion. However, the concentrations required for this effect are higher than those observed in the serum under physiologic conditions. Furthermore, the mechanisms involved in the inhibitory effects of somatostatin remain uncertain. Somatostatin does not seem to exert effects on vagal afferent or efferent pathways but instead has effects on a central vagal site where it can reduce the effects of CCK. Somatostatin also has been reported to reduce the release of secretin and CCK from enteroendocrine cells and it is therefore likely that somatostatin also has a paracrine effect on CCK and secretin release.

PYY and pancreatic polypeptide are also inhibitory hormones. PYY is a 36-amino-acid peptide that is present in the distal small intestine, colon, and rectum and is released by fat and protein in the distal gut. Pancreatic polypeptide (PP) is closely related to PYY, but PP is localized in the islets of Langerhans. The only apparent physiologic actions of PP are the inhibition of pancreatic and biliary secretion. PP secretion is regulated by a cholinergic mechanism. Infusion of either PYY or PP inhibits meal-stimulated pancreatic secretions. These effects appear to be mediated by an influence on central vagal regulation of pancreatic secretion.

## CELLULAR MECHANISMS REGULATING PANCREATIC SECRETION

### Receptors

As described above, hormones and neurotransmitters that stimulate pancreatic secretion may do so by directly regulating acinar and duct cells or by regulating these cells indirectly through nerves or blood vessels. Determination of the physiologic regulatory pathways can be aided by analysis of effects on isolated acinar and duct cells and localization of receptors for each regulator on its target cell. For pancreatic acinar cells, the ability to stimulate amylase secretion *in vitro* is useful for determining the direct effects of agonists and antagonists. The presence of specific receptors has also been confirmed by binding studies with radiolabeled analogues and antagonists. Receptors can also be localized using electron microscopic autoradiography and confocal fluorescence microscopy. Preparations of isolated duct segments or cultured monolayers of duct cells that can be utilized to investigate direct interactions with regulatory molecules have also been developed.

Acinar cells have been found to bear receptors for CCK, bombesin, acetylcholine (m3 muscarinic), $VIP_1$ and secretin. However, important differences exist between species. For example, rodents, but not humans, express $CCK_1$ receptors. CCK interacts with both $CCK_1$ (previously $CCK_A$) receptors, which are highly specific for CCK, and $CCK_2$ (gastrin, previously $CCK_B$) receptors, which respond to both CCK and gastrin. Much is known about $CCK_1$ and m3 receptors and their signaling, because of their presence on rodent acinar cells. CCK receptors on afferent nerves appear to be of the $CCK_1$ type and have properties similar to those on acinar cells. It is more difficult to study the receptors regulating the pancreatic duct cells because of the relatively small number of these cells and the difficulty in studying their physiologic functions (e.g., ion transport) *in vitro*. However, studies have indicated the presence of receptors for secretin, ATP, CCK, VIP, and acetylcholine on these cells.

### Transmembrane Signaling

All major secretagogue receptors are members of the seven hydrophobic transmembrane domain family of receptors that interact with guanine nucleotide-binding proteins (G-proteins) to activate intracellular signaling. The secretagogue receptors couple to the activation of heterotrimeric G-proteins that are composed of three subunits ($\alpha$, $\beta$, and $\gamma$) and are usually defined on the basis of their $\alpha$-subunit. The G-proteins primarily responsible for the stimulation of pancreatic acinar cell secretion are members of the $G_q$ family, which includes $G_q$ and $G_{11}$. These G-proteins regulate secretion through interactions with a phosphoinositide specific phospholipase C, leading to increases in diacylglycerol and inositol trisphosphate and ultimately protein kinase C and $Ca^{2+}$. Other secretagogues, such as secretin, activate $G_s$ proteins. $G_s$ is coupled to the activation of adenylate

cyclase and increases intracellular cyclic AMP (cAMP) and protein kinase A activity. $G_s$-coupled receptors are weak stimulators of acinar cell secretion but have synergistic effects when combined with receptors that activate the $G_q/Ca^{2+}$ pathways.

It should also be noted that secretagogue receptors may have other important actions on pancreatic acinar cells, such as tropic effects or influences on enzyme gene expression, and these effects may involve other signaling pathways. CCK has been reported to activate a wide variety of effector proteins including phospholipase C, phospholipase A2, phospholipase D, protein kinase A, protein kinase C, phosphatidylinositol 3-kinase, focal adhesion kinase, tyrosine kinases, several mitogen-activated protein kinases, and stress-activated protein (SAP) kinase and the nuclear oncogenes c-fos, c-myc, and c-jun.

## Mechanism of Action of Intracellular Messengers

The mechanisms by which increases in intracellular messengers act to induce protein and fluid secretion are not completely understood. It is generally held that second messengers exert their effects by changes in the phosphorylation of regulatory proteins. In addition to protein kinase C and protein kinase A (PKA), which were previously mentioned, several $Ca^{2+}$-activated kinases have been identified in pancreatic acinar cells including $Ca^{2+}$/calmodulin-activated type II and type III kinase and myosin light chain kinase. Pancreatic acinar cells also contain the major classes of serine/threonine phosphatases (i.e., PP1, PP2A, and PP2B), which may also be important for the regulation of pancreatic secretion. One of these, PP2B or calcineurin, is activated by the $Ca^{2+}$/calmodulin complex.

The role of intracellular messengers and effectors in pancreatic enzyme secretion is summarized in Fig. 2. Simulation of secretion normally involves synergistic interactions among intracellular messengers. In the case of acetylcholine and CCK, this includes interactions between $Ca^{2+}$ and diacylglycerol-activated pathways. Agents such as VIP and secretin, which increase cAMP, add a further interaction at the intracellular effector level. Proteins localized on the granule and lumenal plasma membrane and several soluble and cytoskeletal proteins may be involved in exocytosis. In pancreatic duct cells, the same intracellular messengers and kinases regulate ion pumps, carriers, and channels involved in fluid and electrolyte secretion. In this case, the primary intracellular messenger is cAMP, which activates PKA, which phosphorylates cystic fibrosis transmembrane regulator, the ion channel involved in anion egress from duct cells.

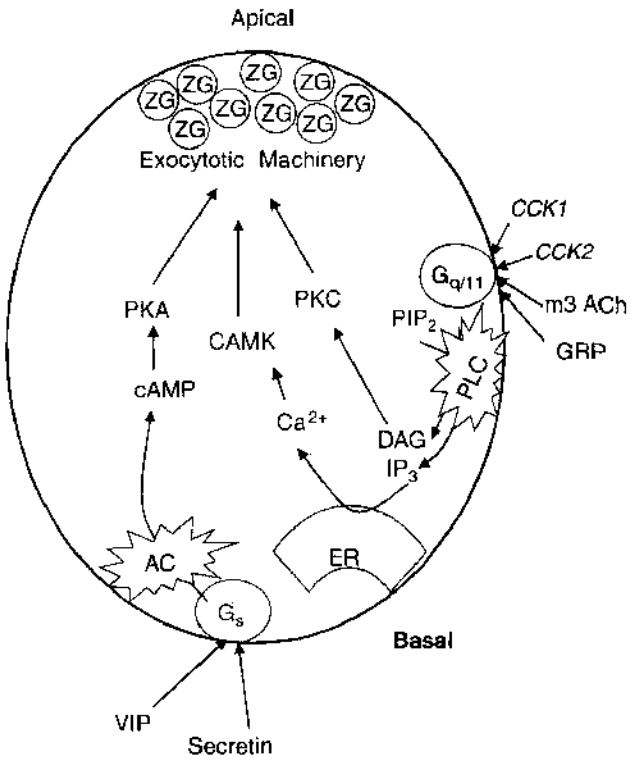


FIGURE 2 Pancreatic acinar cell stimulus–secretion coupling. The pancreatic acinar cell expresses receptors for a variety of molecules that stimulate secretion. Specific high-affinity receptors including muscarinic cholinergic (m3 ACh) and gastrin-related peptide (GRP) receptors, as well as in some species either CCK1 or CCK2 receptors or both, activate G-proteins of the $G_q/G_{11}$ type to activate a phospholipase C (PLC), which converts phosphotidylinositide 1,4-bisphosphate ($PIP_2$) into diacyglycerol (DAG) and inositol 1,4,5-trisphosphate ($IP_3$). $IP_3$ subsequently activates specific receptors on the endoplasmic reticulum (ER) intracellular $Ca^{2+}$ stores, causing an increase in cytoplasmic $Ca^{2+}$. Increased $Ca^{2+}$ activates $Ca^{2+}$-dependent kinases including calmodulin kinase (CAMK). DAG activates protein kinase C (PKC). Other stimulatory molecules, such as the neurotransmitter vasoactive intestinal peptide (VIP) and the hormone secretin, activate specific receptors that are coupled to G-proteins of the $G_s$ type. Activation of $G_s$ stimulates adenylate cyclase (AC) production of cyclic AMP (cAMP). Increased cAMP levels activate protein kinase A (PKA). Increased activity of the various kinases leads to activation of the exocytotic machinery, which includes membrane fusion-related molecules including Rab and soluble N-ethylmaleimide-sensitive attachment protein receptor (SNARE) proteins existing on zymogen granule (ZG) membranes and the apical plasma membrane, as well as cytoskeletal components including actin and microtubule networks.

## Zymogen Granule Exocytosis

The terminal steps in protein secretion involve exocytotic release of enzymes from zymogen granules. This involves a membrane fusion event between zymogen granules and the apical plasma membrane. Membrane

fusion involves a number of specific membrane-associated proteins of the soluble *N*-ethylmaleimide-sensitive attachment protein receptor (SNARE) family and Rab families. The actin cytoskeleton is also involved in exocytosis, serving alternately as a barrier, preventing premature secretion, and as a potential motile element. Microtubules are also involved in the movement of zymogen granules to the apical portion of the cell, where they can interact with the exocytotic machinery.

## SUMMARY

In summary, pancreatic exocrine secretion is regulated by a complex interplay of nervous, hormonal, and paracrine regulation that matches fluid, bicarbonate, and enzyme levels to meet physiologic demands. Complex interactions occur between multiple regulatory molecules and signaling pathways. The relative contribution of various components to the overall secretory function varies with the phase of secretion. Significant species differences occur with regard to receptor localization and the importance of different arms of the regulatory mechanisms.

## See Also the Following Articles

**Cholecystokinin (CCK) • Enteroglucagon • Exocytosis • Gastrin • Gastrin-Releasing Peptide • Pancreatic Bicarbonate Secretion • Pancreatic Digestive Enzymes • Pancreatic Polypeptide Family • Pituitary Adenylate Cyclase Activating Peptide (PACAP) • Secretin • Vasoactive Intestinal Peptide (VIP)**

## Further Reading


Chey, W. Y., and Chang, T. (2001). Neural hormonal regulation of exocrine pancreatic secretion. *Pancreatology* **1**, 320–335.

Lee, M. G., Ahn, W., Lee, J. A., Kim, J. Y., Choi, J. Y., Moe, O. W., Milgram, S. L., Muallem, S., and Kim, K. H. (2001). Co-ordination of pancreatic $HCO_3^-$ secretion by protein–protein interaction between membrane transporters. *J. Pancreas* **2**, 203–206.

Logsdon, C. D. (1999). Role of cholecystokinin in physiologic and pathophysiologic growth of the pancreas. *In* "Gastrointestinal Endocrinology" (G. H. Greeley, Jr., ed.), Chap. 15, pp. 393–422. Humana Press, Totowa, NJ.

Naruse, S., Kitagawa, M., Ishiguro, H., and Hayakawa, T. (2002). Feedback regulation of pancreatic secretion by peptide YY. *Peptides* **23**, 359–365.

Niebergall-Roth, E., and Singer, M. V. (2001). Central and peripheral neural control of pancreatic exocrine secretion. *J. Physiol. Pharmacol.* **52**, 523–538.

Owyang, C. (1996). Physiological mechanisms of cholecystokinin action on pancreatic secretion. *Am. J. Physiol.* **271**, G1–G7.

Owyang, C., and Williams, J. A. (1999). Pancreatic secretion. *In* "Textbook of Gastroenterology" (T. Yamada, ed.), Chap. 16, pp. 355–379. Lippincott, Williams & Wilkins, Philadelphia, PA.

Solomon, T. E. (1994). Control of exocrine pancreatic secretion. *In* "Physiology of the Gastrointestinal Tract" (L. R. Johnson, ed.), Chap. 41, pp. 1499–1530. Raven Press, New York.

Spannagel, A. W., and Green, G. M. (1999). Pancreatic hypersecretion in the jejunal-bypass rat. *Pancreas* **18**, 47–52.

Wasle, B., and Edwardson, J. M. (2002). The regulation of exocytosis in the pancreatic acinar cell. *Cell Signal.* **14**, 191–197.

Williams, J. A. (2001). Intracellular signaling mechanisms activated by cholecystokinin-regulating synthesis and secretion of digestive enzymes in pancreatic acinar cells. *Annu. Rev. Physiol.* **63**, 77–97.

Yule, D. I., and Williams, J. A. (1994). Stimulus-secretion coupling in the pancreatic acinus. *In* "Physiology of the Gastrointestinal Tract" (L. R. Johnson, ed.), 3rd Ed., Chap. 39, pp. 1447–1472. Raven Press, New York.

# Pancreatic Function Tests

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**bentiromide test** Tubeless pancreatic function test that indirectly measures pancreatic chymotrypsin output using bentiromide as a substrate.
**cholecystokinin** Gastrointestinal hormone that stimulates secretion of digestive enzymes by pancreatic acinar cells.
**chronic pancreatitis** Clinical diagnosis reflecting permanent or progressive deterioration in pancreatic function or structure or both.
**fecal pancreatic elastase I** Tubeless pancreatic function test that directly measures fecal pancreatic elastase I in stool.
**malabsorption** Impaired intestinal absorption of micronutrients due to either intestinal disease or maldigestion.
**maldigestion** Impaired digestion of macronutrients (i.e., fat), as in pancreatic insufficiency.
**secretin** Gastrointestinal hormone that stimulates secretion of bicarbonate and water by pancreatic ductal cells.

**The exocrine function of the human pancreas is to secrete digestive enzymes that aid in absorption of dietary nutrients. Tests to measure pancreatic secretions can be invasive, requiring insertion of tubes to collect pancreatic fluids, or noninvasive, requiring oral administration of compounds and subsequent assays of stool, blood, urine, or breath components.**

## INTRODUCTION

Pancreatic function tests are used to measure pancreatic secretion in humans. The tests are clinically useful to discriminate between pancreatic and nonpancreatic causes of malabsorption. Pancreatic malabsorption occurs when residual pancreatic enzyme secretion is only 5–10% of normal levels, as occurs in severe chronic pancreatitis, when tests of pancreatic function are frequently abnormal. Both invasive and noninvasive tests exist. The most sensitive and specific tests, the secretin and cholecystokinin (CCK) stimulation tests, are invasive in that they require placement of a gastroduodenal tube; they are also time-consuming (2 - 3 hours) and are performed in only a few medical centers. "Tubeless" tests are more efficient, but, unfortunately, their clinical use is limited by their relative insensitivity to detecting mild impairments in pancreatic function, as in early chronic pancreatitis, when the secretin or CCK test may be abnormal.

## TESTS REQUIRING A GASTRODUODENAL TUBE

Secretin and cholecystokinin are gastrointestinal hormones that may be given alone or together to stimulate and measure pancreatic secretion directly. This protocol, which is primarily used in research, requires placement of a double-lumen tube (Dreiling tube), which is anatomically positioned using fluoroscopy. The gastric aspiration port is positioned in the distal stomach for removal of contaminating gastric juice, while the duodenal aspiration port is positioned in the first, second, and third segments of the duodenum for removal of pancreatic juice under continuous suction. Juice removed from the duodenal port is used for analysis of pancreatic secretion, including measurements of pancreatic juice volume and bicarbonate concentration for the secretin test and trypsin and lipase output for the CCK test. For example, either in response to meals (the Lundh test) or to intravenous secretin administration, both pancreatic juice flow and juice bicarbonate concentration increase. A peak bicarbonate fluid concentration of less than 80 mEq/liter of bicarbonate indicates impaired pancreatic secretory function, suggestive of chronic pancreatitis. However, a positive test (and impaired pancreatic secretion) may occur in the absence of clinical or radiologic features of chronic pancreatitis, in conditions such as diabetes mellitus, protein-calorie malabsorption, gastric surgery, truncal vagotomy, celiac sprue, and hepatic cirrhosis.

## TUBELESS TESTS

Noninvasive tubeless pancreatic function tests indirectly measure pancreatic function by relying on two bioassay principles. Patients with chronic pancreatitis may produce insufficient pancreatic digestive enzymes (e.g., lipase, chymotrypsin, amylase, elastase, and trypsin), causing maldigestion and poor absorption of foods (e.g., fat, protein, and carbohydrates), which may be measured in the stool. Alternatively, oral administration of a synthetic compound that is acted on by a specific pancreatic digestive enzyme will generate a product that may be measured in stool, blood, breath, or urine.

 

Diminished recovery of the product suggests impaired pancreatic enzymatic activity. Insensitivity and failure to detect mild disease is a problem common to all tubeless tests; bioassays in these protocols are able to distinguish reliably only among patients with moderate and severe pancreatic insufficiency. In addition, these tests are not always specific to pancreatic function; patients with normal pancreatic secretion may have a positive test result if they have hepatobiliary disease or small bowel diseases causing malabsorption (i.e., celiac sprue, Crohn's disease, or Whipple's disease) or have had prior gastric surgery.

As illustration of a tubeless test, the bentiromide test indirectly measures pancreatic chymotrypsin output. Endogenous chymotrypsin, a pancreatic digestive enzyme, cleaves orally administered bentiromide (*N*-benzoyl-L-tyrosyl-*p*-aminobenzoic acid), liberating *para*-aminobenzoic acid (PABA), which is absorbed, hepatically metabolized, and excreted in urine. Decreased recovery occurs in patients with inadequate pancreatic function, as in chronic pancreatitis. Many medications interfere with urinary measurements of free PABA and its metabolites and should be discontinued 3 days prior to the test. Because renal dysfunction lowers urinary recovery of PABA, measurement of PABA in serum rather than in urine has been developed with similar test sensitivity. An alternative but similar tubeless test is the fluorescein dilaurate (pancreolauryl) test, which measures nonspecific lipase (cholesterol esterase) activity and is slightly more sensitive than the bentiromide test.

Measurement of fecal pancreatic elastase 1 is the most commonly used tubeless test in the United States and Europe but is nonetheless controversial, because it has not been shown to be consistently sensitive or specific for mild or moderately impaired pancreatic secretion. The test is simple, relatively inexpensive, and involves measuring human fecal pancreatic elastase by enzyme-linked immunosorbent assay (ELISA). Unlike other pancreatic digestive enzymes, fecal pancreatic elastase levels do not change during intestinal transit, are stable in stool samples for up to 1 week, and are unaffected by concurrent use of oral pancreatic enzyme replacement therapy.

## SUMMARY

Tubeless pancreatic function tests are useful for diagnosis of chronic pancreatitis in the setting of malabsorption, when the pancreas is severely damaged. In the setting of mild to moderate disease (when malabsorption is not present), the clinical utility of these tests is less well defined due to poor test sensitivity. In this situation, when a diagnosis is necessary to achieve patient management, the invasive secretin and CCK stimulation tests are preferred, if available.

### See Also the Following Articles

**Amylase • Cholecystokinin (CCK) • Pancreatic Triglyceride Lipase • Pancreatitis, Chronic • Secretin • Trypsin**

### Further Reading

Chey, W. D., and Chey, W. Y. (1999). Tests of gastric and exocrine pancreatic function and absorption. *In* "Textbook of Gastroenterology" (T. Yamada *et al.*, eds.), 2nd Ed., Vol. 1, pp. 2924–2937. Lippincott Williams & Wilkins, Philadelphia.

DiMagno, E. P. (1998). A perspective on the use of tubeless pancreatic function tests in diagnosis. *Gut* 43(1), 2–3.

Owyang, C. (1999). Chronic pancreatitis. *In* "Textbook of Gastroenterology" (T. Yamada *et al.*, eds.), 2nd Ed., Vol. 1, pp. 2151–2177. Lippincott Williams & Wilkins, Philadelphia.

# Pancreatic Polypeptide Family

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**enteroendocrine cell** A specialized epithelial cell diffusely distributed throughout the gut epithelieum that releases a hormone after exposure to luminal contents and other stimuli.

**enterogastrone** Intestine-derived factor released in response to intestinal fat; inhibits gastric acid secretion when administered at physiologic levels.

**interdigestive motility complex** A cyclic, periodic pattern of gastric and intestinal contraction during the fasting state characterized by four phases: no activity (Phase 1), uncoordinated activity (Phase 2), a brief period of sweeping peristaltic contractions (Phase 3), and a period of uncoordinated activity preceeding Phase 1 (Phase 4).

**prepro hormone** The precursor peptide containing all the hormone gene-encoded amino acids (including the signal peptide) before processing to the mature peptide.

**The pancreatic polypeptide family of peptides consists of pancreatic polypeptide, peptide YY, and neuropeptide Y. These peptides share significant features of gene organization, amino acid sequence, three-dimensional structure, and receptor binding specificity. However, pancreatic polypeptide and peptide YY are restricted to endocrine cells of the pancreas and distal gut epithelium and are released in response to meals. Neuropeptide Y is restricted to neural tissue and is released by nerve stimulation in the manner of a neurotransmitter. Pancreatic polypeptide and peptide YY generally exert inhibitory effects on gut function, such as gastric acid secretion and gastrointestinal motility, in order to regulate the postprandial state. Neuropeptide Y is better known for its effects on the cardiovascular, endocrine, and central nervous systems, but it also exerts inhibitory effects on gut secretion and motility.**

## INTRODUCTION

The pancreatic polypeptide family of peptides includes pancreatic polypeptide (PP), peptide YY (PYY), and neuropeptide Y (NPY). These peptides are related by a high degree of sequence homology among their 36 amino acids as well as by a shared hairpin-like tertiary structure. These similarities are thought to reflect origins from common ancestral genes, gene duplications resulting in new peptides, and peptide sequence conservation related to evolutionary pressures. However, there has been significant divergence of distribution, production, and actions of these peptides, with PP and PYY produced by endocrine cells of the pancreas and the gut epithelium, respectively, and NPY produced by neurons in the peripheral and central nervous systems.

## Family Discovery

Pancreatic polypeptide was the first family member to be purified and identified by amino acid sequence following its recognition as a persistent contaminant of insulin preparations. In contrast, peptide YY and neuropeptide Y were both discovered using a strategy to isolate novel peptides that have been amidated at their C terminus, a biochemical modification often indicating innate bioactivity in peptides. Peptide YY and neuropeptide Y were isolated from extracts of porcine intestine and brain, respectively. The purification and amino acid sequence of all of these peptides were completed in advance of establishing their biological effects.

## Peptide Structure

The three-dimensional structures of the peptides in this family, deduced from crystallography and molecular modeling, have helped to explain the stability of these molecules and the specificity of interaction with receptor proteins. The structure is best described as two helices running antiparallel to each other; there is a polyproline type II helix (amino acids 1–8) connected to an $\alpha$ helix (amino acids 14–32) connected by a type I $\beta$ turn and stabilized by hydrophobic interactions between the helices. The C-terminal hexapeptide is flexible, projecting from the base of the molecule. Much of the receptor binding specificity is found in the close approximation of amino acid residues from the two ends of the molecule, as well as the terminal hexapeptide composition.

 

## PANCREATIC POLYPEPTIDE

### Tissue Distribution

Pancreatic polypeptide expression is restricted to endocrine cells found predominantly in the pancreas, where they can exist as part of the endocrine islets or as single or groups of cells in the exocrine pancreatic tissue, and less often in the epithelium of pancreatic ducts. The density of PP-containing cells is highest in the pancreatic head, and the tissue concentration of PP is five to eight times higher in the pancreatic head compared to the tail. The PP-immunoreactive cells have also been reported in the gastric mucosa of some adult mammals (dog, cat, opossum) and in the human colon.

### Gene Organization

The human gene for pancreatic polypeptide is made up of four exons and three introns that encode the 95-amino-acid pancreatic polypeptide prepro hormone. Exon 1 encodes the 5′ untranslated region, exon 2 encodes a 29-amino-acid signal peptide and PP, exon 3 encodes a 23-amino-acid extension, and exon 4 encodes a further 7-amino-acid extension and the 3′ untranslated region. Posttranslational processing produces the 36-amino-acid peptide with an amidated C-terminal tyrosine residue.

### Mechanisms of Pancreatic Polypeptide Release

Pancreatic polypeptide is primarily released following nutrient ingestion and requires an intact vagus nerve for full response. PP release occurs with all phases of feeding, including the cephalic, gastric, and intestinal phases. The cephalic phase, induced by sham feeding in animals or spit-and-chew techniques in humans, stimulates between 10 and 20% of the total meal-stimulated PP response. The cephalic-phase release of PP enhances further PP release during the gastric and intestinal phases that follow. The early phases of meal-stimulated PP release depend on vagal input. The cephalic-phase PP release is blocked by anticholinergic drugs and truncal vagotomy. Similarly, gastric distension resulting in PP release is blocked by anticholinergic drugs and vagotomy. Vagal activity, whether by direct electrical vagal stimulation or stimulation by insulin hypoglycemia, can increase PP serum levels.

In contrast, the intestinal phase of the feeding response, simulated by administering nutrients directly into the duodenum, does not depend on the neural reflexes mediating the cephalic phase and gastric distension responses. Although intestinal-phase PP release is optimized by intact vagal inputs, it still occurs after vagotomy, likely through remaining local enteric–pancreatic neural reflexes. Moreover, it is thought that intestinal-phase feeding also involves other nutrient-stimulated hormones—cholecystokinin (CCK), for instance—that contribute to the later increases in meal-induced PP release. The hormonal regulation of PP release during intestinal digestion is complex and not well defined.

Serum pancreatic polypeptide levels in the fasting state vary rhythmically with the hormonal and motility events that characterize the interdigestive motility complex. Basal PP levels peak through phases 1 to 3 and then return to low levels during phase 4. These basal PP level fluctuations are abolished by local ganglionic blockade and anesthetic use, supporting a role for neural reflexes in this response. Finally, average basal (fasting) pancreatic polypeptide levels increase with age.

### Pancreatic Polypeptide Receptors

The Y4 receptor, the high-affinity receptor for pancreatic polypeptide, has been cloned and sequenced from many mammalian species, including rodents, pigs, and humans. The Y4 receptor is a member of the G protein-coupled receptor superfamily, and Y4 receptors have dissociation constants in the range of 20–40 pM for same-species cognate ligands (human PP for the human PP receptor, for instance). However, Y4 receptors are only PP preferring and not PP specific, allowing binding of PYY and NPY peptides at 100-fold lower affinities. In certain species, PP binds to the Y5 receptor (human and bovine PP have high binding affinity, and rat PP has low binding affinity, for the rat PP Y5 receptor), although with lower affinity than NPY or PYY. Last, lower vertebrates possess a PP receptor that also recognizes PYY.

Pancreatic polypeptide receptors have been reported in the gut, pancreas, brain (hypothalamus, hippocampus, and vagal nuclei of the brain stem), and kidney of various species.

### Pancreatic Polypeptide Biological Actions

There is limited understanding of the physiologic role of pancreatic polypeptide. Two biologic effects that pancreatic polypeptide exerts in a number of species are inhibition of exocrine pancreatic secretion and inducing relaxation of the gallbladder. When PP is administered to produce serum levels attainable after meals, stimulated pancreatic enzyme secretion in dogs and humans is inhibited. Reduced bilirubin secretion into the duodenum after PP infusion is also noted in humans, and decreases in intraluminal gallbladder pressure (pigs) and increased gallbladder filling are seen in animal models. Because these effects occur at

nonpharmacologic serum levels, they are interpreted as being possibly physiologic responses. The effect on the pancreas could act as a negative feedback signal to turn off meal-stimulated pancreatic secretion and the gallbladder effect could preserve extrahepatic bile excretion between meals.

Other effects attributed to PP include inhibition of gastric secretion (at high doses in dogs; no effect at lower doses in humans), modulation of gastric emptying, and modest inhibition of feeding when administered peripherally (accompanied by decreased gastric emptying) and stimulation of feeding when given centrally (accompanied by increased gastric emptying). However, hypersecretion of PP in humans due to PP-producing tumors produces no symptoms, and elevated PP levels in rats transgenic for the PP gene are associated with only modest inhibition in food intake and gastric emptying. On the other hand, patients with Prader–Willi syndrome (congenital obesity, hyperphagia, hyperglycemia, and hyperinsulinemia) have abnormally low basal and meal-stimulated levels of PP; PP administration can diminish their hyperphagia through an unknown mechanism.

## PEPTIDE YY

### Tissue Distribution

Peptide YY is predominantly expressed in endocrine cells but is also produced by neurons in certain species. The primary source of serum PYY released into the bloodstream is enteroendocrine cells in the distal gut epithelium; PYY-immunoreactive cells can be found in the upper small intestine of many mammals, but the concentration of these cells increases in an aboral direction, whereby the colon and rectum have the highest density of PYY-producing cells. The PYY-containing cells have a flasklike appearance characteristic of open-type endocrine cells, with a wide base containing the secretory granules and a thin apical arm extending to the gut lumen. A large proportion of the PYY-containing granules also contain proglucagon-derived peptides such as glicentin and glucagon-like peptides 1 and 2.

PYY is also contained in endocrine cells in the gastric mucosa of a few adult animal species, but these are a minor proportion of total PYY-containing cells. PYY can colocalize with glucagon (rats and mice) and PP (dogs and pigs) in pancreatic endocrine cells and in specialized epithelium of alveolar ducts (Syrian golden hamsters). Peptide YY has been found in neural structures of the enteric nervous system, including myenteric ganglia and serosal ganglia. Central nervous system localization of PYY has also been made in the hypothalamus, brain stem, and spinal cord of the rat.

### Gene Organization

The human gene for peptide YY is also made up of four exons and three introns that span approximately 1.2 kb and encode a 97-amino-acid prepro hormone. Exon 1 encodes the 5′ untranslated region, exon 2 encodes a 28-amino-acid signal peptide and most of PYY, exon 3 encodes the C-terminal PYY tyrosine and a 26-amino-acid extension, and exon 4 encodes a further 7-amino-acid extension and the 3′ untranslated region. Posttranslational processing produces the 36-amino-acid peptide with an amidated C-terminal tyrosine residue. The structure of this gene is so similar to that of the human PP gene that it is thought to be the result of a gene duplication event.

Peptide YY has also been discovered to exist as a 34-amino-acid peptide, PYY 3–36, in some species, including humans. This shortened form is likely due to proline dipeptidyl peptidase IV digestion of the full-length peptide. PYY 3–36 can account for up to 50% of total PYY activity in postprandial human serum, and has affinity for Y receptors that bind C-terminal fragments of PYY and NPY. Last, the prostate- and testis-restricted 33-amino-acid human seminal plasmin peptide (so-called PYY2) is homologous to the 12 amino-terminal residues of human PYY, but does not appear to have binding activity at Y receptors.

### Mechanisms of Peptide YY Release

Peptide YY is released in response to ingested food, presumably to coordinate postprandial gastrointestinal reflexes. In humans, PYY serum levels begin to increase within 30 minutes of a meal and reach a plateau after 1–2 hours. The maximum level is maintained for up to 4 hours and then returns slowly to baseline. It is hypothesized that the early increase is due to signals from the duodenum because ingested nutrients have not had time to reach the distal gut for direct stimulation of PYY-containing cells. There are data to support a neurohumoral mechanism regulating PYY release from the distal gut by upper intestinal stimuli, but this is only found in certain species.

There is evidence that gastrin and CCK may be involved in the early postprandial PYY release. Gastric acid secretion stimulated by meals (in dogs) contributes to gastric-phase PYY release because early PYY release can be blocked by histamine receptor blockade and proton pump inhibitors. Gastrin has been found to inhibit PYY release from intestinal endocrine L cells, so the inhibition of gastrin release accompanying gastric acid secretion may remove this inhibitory input on PYY secretion. In rats treated with proton pump inhibitors the resulting increases in gastrin levels are thought to

be responsible for the decrease in PYY content and mRNA levels in the colon because this effect is blocked by a gastrin/CCK-B receptor antagonist. Furthermore, in dogs, CCK infusion increases PYY levels, and this effect can be blocked by CCK-A receptor antagonists. It is not clear if CCK acts directly on PYY-secreting cells or via intermediate neural pathways.

Neural factors play a role in physiologic PYY release. For instance, there may be a baseline inhibitory effect of intact gut innervation on PYY release because truncal vagotomy, general anesthesia, and jejunoileal denervation enhance meal-stimulated PYY release in dogs. On the other hand, a PYY-releasing signal from the duodenum to the distal gut can be interrupted by atropine (in dogs, not rats), hexamethonium (dogs and rats), truncal vagotomy (rats), and CCK receptor antagonists (dogs, not rats). In addition, adrenergic, cholinergic, and certain peptidergic (bombesin, gastrin-releasing peptide) stimuli have been shown to stimulate PYY release, but the physiologic relevance of this is unknown.

The majority of postprandial PYY release is related to exposure of the distal small bowel and colon to the luminal remnants of a meal. In humans, peptide YY is released in proportion to the calorie content (higher levels with more calories) and nutrient composition of a meal (fat meals stimulate significantly more PYY release compared to isocaloric protein or carbohydrate meals). This is consistent with the effect on PYY release following direct instillation of specific nutrients into the distal gut. Administration of oleic acid to distal intestinal epithelium can result in PYY release (seen in dog, cat, rat, and human models). However, the most consistent effect is seen with combinations of oleic acid and bile salts, specifically taurocholate and deoxycholate; oleic acid by itself may have no effect on PYY release (in humans, for instance). Although bile salts enhance the effect of fatty acids on PYY release via direct epithelial contact, they can also have similar stimulatory effects on their own. Glucose and protein or amino acids can also stimulate PYY release after instillation into the distal gut, but whether this is of physiologic importance is not known. Last, adenylyl cyclase-coupled stimuli increasing intracellular cyclic AMP levels appear to be the predominant signals for directing PYY release.

## Peptide YY Receptors

Peptide YY is a high-affinity cognate ligand for several Y receptor subtypes, including the Y1, Y2, and Y5 receptors. Y1 receptors have high affinity for PYY, neuropeptide Y, and specific substituted forms of these peptides, [$Pro^{34}$]PYY and [$Pro^{34}$]NPY, and low affinity for C-terminal fragments of these peptides as well as intact PP. In addition to widespread distribution in the central nervous system, Y1 receptors are also found in veins and arteries as well as in colonic epithelial cells and nerve fibers and ganglia of the enteric nervous system in humans. Y2 receptors display high affinity for PYY, NPY, and various of their C-terminal fragments; compared to the Y1 receptor, there is low-affinity binding of [$Pro^{34}$]-PYY and [$Pro^{34}$]NPY and no binding of PP. Y2 receptors occur in the brain, but also in the colonic epithelium of rats, in blood vessels (dog saphenous vein), and in nerve fibers of the autonomic nervous system. The Y5 receptor is described as "Y1-like" because not only do PYY and NPY bind with high affinity, but so do the Y1 analogues ([$Pro^{34}$]PYY and [$Pro^{34}$]NPY) in addition to long C-terminal fragments such as NPY 2–36 and PYY 3–36; however the C-terminal fragment NPY 13–36 binds with much lower affinity (PP binding affinity for the rat and human Y5 receptor was low for rat PP but high for human and bovine PP). The Y5 receptor subtype is found primarily in the brain.

Other reported receptors for PYY include the Y6 receptor and a PYY-preferring receptor. The Y6 receptor was originally found in rat brain and subsequently rabbit, monkey, and human homologues were described. The rat Y6 receptor has been variably shown to possess a high affinity for PYY with a Y1-like binding profile or a high affinity for PP and lower affinity for PYY. The Y6 receptor has not been shown to be a physiologically relevant receptor in humans. A PYY-preferring receptor has been suggested to exist because of a three to five times greater potency compared to NPY for some biological effects, but this purported receptor has not been characterized molecularly and remains theoretical at present.

## Peptide YY Biological Actions

Peptide YY has been characterized as a candidate enterogastrone but additionally has been shown to inhibit intestinal motility, gut epithelial secretion, and pancreatic secretion. There are several aspects of interpretation of the large body of data pertaining to the biological effects of PYY that must be kept in mind; although similar effects for PYY are seen in many animal models, the ultimate effect of PYY is very dependent on (1) the species studied, (2) whether resting or stimulated conditions are tested for PYY inhibitory effects (and the type of stimulation used), and (3) what doses of PYY are required for effects (whether effects of PYY are observed at postprandial serum concentrations or only at higher, so-called pharmacologic, doses).

Whether PYY acts as a classic enterogastrone is not clear. On the one hand, it has been shown that

intravenous administration of PYY at doses reproducing higher postprandial levels and supraphysiologic levels can inhibit gastric acid production in humans, rats, and dogs. On the other hand, the inhibition of gastric acid production and emptying induced by introducing fat into the upper small intestine is not due to the accompanying PYY elevations (in humans and dogs) but is due to other factors, such as CCK. On its own, PYY is most potent at inhibiting cephalic-phase gastric acid production (nearly 90% inhibition in sham-fed dogs), and this requires vagal innervation. PYY can also inhibit gastric acid production by additive effects with glucagon-like peptide-1, secretin, and somatostatin or by directly blocking gastrin-stimulated histamine release from enterochromaffin-like (ECL) cells (in rats).

PYY can also act in the central nervous system (CNS) to modulate gastric acid secretion. However, the route of access of PYY to the CNS results in different effects on gastric acid production. It has been shown that intravenous PYY can cross the blood–brain barrier to bind specifically to regions of the dorsal vagal complex (DVC) [the nucleus tractus solitarii, the dorsal motor nucleus (DMN) of the vagus, and the area postrema (AP)], where Y receptor subtypes Y1, Y2, and Y4 have been found. The inhibitory activity of PYY on centrally stimulated gastric acid secretion (cephalic phase, for instance) may occur within the CNS because intracisternal injection of neutralizing antibodies against PYY can block its inhibitory effects. On the other hand, when PYY is directly microinjected into the DVC of rat brain stem, there is a dose-dependent increase in gastric acid secretion (that is dependent on an intact vagus nerve). These observations suggest that PYY has a complex role in gastric acid regulation that varies with the phase of gastric acid production.

One of the most consistently observed effects of PYY is the inhibition of intestinal motility. This effect is thought to enhance intraluminal nutrient digestion and absorption, earning PYY the rubric "the ileal brake." Delays in orocecal transit time are induced by PYY infusions that reproduce normal postprandial PYY levels. The decrease in intestinal motility following fat exposure in the lower small bowel can be blocked by neutralizing serum PYY with specific antisera. This effect on intestinal motility may be beneficial in conditions resulting in delivery of unabsorbed nutrients to the distal bowel and colon, such as pancreatic insufficiency, Crohn's disease, and acute diarrhea, which are associated with high basal and postprandial PYY levels.

In the pancreas, supraphysiologic levels of PYY can inhibit secretin-stimulated secretion in the anesthetized cat. Similarly, high doses of intravenous PYY inhibit meal- and secretin-stimulated pancreatic secretion in the dog, but porcine PYY has no effect on secretin- or CCK-stimulated pancreatic secretion in humans.

Other PYY biological effects in the gut include inhibition of stimulated apical chloride secretion in gut epithelium and an increase in intestinal absorption in intact animals. PYY has been shown to stimulate proliferation in gut epithelium (Y receptors are expressed by the gut epithelium of humans, rabbits, and rats) and may be involved in gut epithelial differentiation signals. PYY effects on feeding behavior are included in the discussion of neuropeptide Y.

## NEUROPEPTIDE Y

### Tissue Distribution

The majority of neuropeptide Y is found in the central and peripheral nervous systems (also seen in chromaffin cells of the adrenal medulla and pheochromocytomas), so that its distribution in the gut is within nerve cells and fibers. The NPY-immunoreactive (NPY-IR) nerves in the gut may be intrinsic or extrinsic to the gut. The intrinsic NPY-IR nerves are part of the nonadrenergic enteric nervous system, where NPY may colocalize with other neuropeptides, such as vasoactive intestinal peptide (VIP) and peptide histidine isoleucine. The extrinsic NPY-IR nerves generally are adrenergic fibers where NPY colocalizes with norepinephrine, and they innervate vascular structures. NPY is found in ganglia cell bodies, with higher frequency in submucosal plexi but also occurring in the myenteric plexi and extrinsically in the celiac ganglion. NPY-IR nerve fibers are found extending from plexi to the muscle layers of the muscularis propria, as well as within the muscularis mucosa, and into the mucosa, where they may closely invest the crypts. Perivascular NPY-IR fibers are largely of extrinsic adrenergic origin.

### NPY Gene Expression and Receptors

The human gene for neuropeptide Y is also made up of four exons and three introns that span approximately 8 kb and encode 97-amino-acid residues of the NPY prepro hormone. Exon 1 encodes the 5′ untranslated region, exon 2 encodes residues 1–28 of the signal peptide and most of NPY, exon 3 encodes the C-terminal tyrosine, the 3-amino-acid cleavage site, and a 23-amino-acid extension, and exon 4 encodes a further 7-amino-acid extension and the 3′ untranslated region. Posttranslational processing produces the 36-amino-acid peptide with an amidated C-terminal tyrosine residue.

The full-length amidated 36-amino-acid peptide is the major form of NPY found in the bloodstream after

release from nerve endings following sympathetic stimulation or feeding. NPY binds to several Y receptor subtypes as previously discussed. An NPY-specific receptor subtype, Y3, that does not bind PYY has been described pharmacologically but has yet to be cloned. Given the extensive representation of NPY in nerves in the gut, it is important to note that Y receptors are found on ganglion cells and nerve fibers (in humans) and on epithelial cells (in rabbits, humans, rats, and mice), where NPY released from nerve endings (and possibly PYY released from enteroendocrine cells) could exert an effect.

## NPY Biological Actions

Neuropeptide Y has a wide variety of activities, including vasoconstriction and regulation of cardiac function, stimulation of feeding, modulation of pituitary release of hormones, and effects on circadian rhythm and anxiety state. In the gut, administration of NPY potently inhibits mucosal fluid and electrolyte secretion stimulated by prostaglandin E2, VIP, and cholera toxin. NPY has effects on gut motility as well, mediating contraction and relaxation of the lower esophageal sphincter (cat), contraction of longitudinal muscle and inhibition of peristalsis and circular muscle reflex contraction (guinea pig), and contraction of longitudinal muscle (rat, dog). NPY appears to mediate its effects on motility not by direct actions on muscle but rather by inhibition of excitatory neurons of the enteric nervous system.

Neuropeptide Y has emerged as one of the key neuropeptides active in stimulating feeding behavior and coordinating peripheral signals involved in body weight regulation. Studies in rodents show that NPY injected into the brain (cerebral ventricles and hypothalamus) induces feeding, prolongs feeding, and causes feeding to resume in fed animals. Increases in endogenous NPY occur in the paraventricular nucleus of the hypothalamus prior to nocturnal feeding, during fasting, and accompanying the hyperphagia of drug-induced diabetes and genetically obese animals such as fatty Zucker rats and *ob/ob* mice. These latter observations suggest that NPY plays a physiologic role in feeding behavior. Current models of NPY-induced feeding show that the NPY released from fibers originating in the hypothalamic arcuate nucleus is responsible for stimulating feeding. The stimulation of feeding appears to be mediated through Y1 or Y5 receptor subtypes, likely located in other hypothalamic areas such as the paraventricular nucleus. Though rises in NPY levels in the hypothalamus precede feeding, it is not yet clear what the exact proximate mechanisms are that control and coordinate this increase.

Neuropeptide Y-stimulated feeding may also be part of a larger regulatory mechanism that is influenced by signals from outside the central nervous system. It has been shown that activation of Y2 receptor subtypes in the rat hypothalamus can decrease the release of NPY. In support of this activity, a Y2-preferring ligand PYY 3–36 can inhibit nocturnal onset feeding in rats (injected intraperitoneally) and decrease calorie intake in humans following intravenous infusions that mimic postprandial blood levels. This suggests that peripheral postprandial PYY release (recall the PYY 3–36 fragment can account for up to 50% of total PYY activity in postprandial human serum) may contribute to a satiety effect by attenuating the NPY effect in the hypothalamus. Whether this inhibitory effect is accomplished by direct effects on the hypothalamus or indirectly via other neural mechanisms has yet to be established.

Leptin is another peripheral signal related to regulation of body weight that can influence hypothalamic NPY activity. Leptin can decrease the production of NPY in the arcuate nucleus of the hypothalamus (mice); subpopulations of NPY-containing neurons in the rat hypothalamus involved in reactions to fasting also express the leptin receptor, supporting a role for leptin regulation of NPY in feeding response. It is thought that fluctuations in leptin levels related to body fat stores may contribute to enhanced NPY-induced feeding during low-body-fat conditions (low leptin levels) and blunted NPY-induced feeding during high-body-fat states (high leptin levels).

These data suggest that NPY has an important role in central control of feeding behavior and that peripheral signals, including postprandial PYY release and leptin levels related to body fat stores, modulate the feeding response to establish satiety and energy homeostasis.

## See Also the Following Articles

**Cholecystokinin (CCK) • Gastric Acid Secretion • Gastric Motility • Gastrin • Ileal Brake • Pancreatic Enzyme Secretion (Physiology)**

## Further Reading

Blomqvist, A. G., and Herzog, H. (1997). Y-Receptor subtypes—How many more? *Trends Neurosci.* 20, 294–298.

Cerda-Reverter, J. M., and Larhammar, D. (2000). Neuropeptide Y family of peptides: Structure, anatomical expression, function, and molecular evolution. *Biochem. Cell Biol.* 78, 371–352.

Mannon, P., and Taylor, I. L. (1994). The pancreatic polypeptide family. *In* "Gut Peptides: Biochemistry and Physiology" (J. H. Walsh and G. J. Dockray, eds.), pp. 341–370. Raven Press., New York.

Michel, M. C., Beck-Sickinger, A., Cox, H., Doods, H. N., Herzog, H., Larhammar, D., Quirion, R., Schwartz, T., and Westfall, T. (1998). XVI. International union of pharmacology recommendations for the nomenclature of neuropeptide Y, peptide YY, and pancreatic polypeptide receptors. *Pharmacol. Rev.* 50, 143–150.

# Pancreatic Pseudocysts

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**computerized tomography** A radiographic technique allowing visualization of a plane or section through the body.
**endoscopic retrograde cholangiopancreatography** A procedure whereby pancreatic and biliary ducts are visualized by endoscopic injection of contrast medium.
**pseudocyst** A non-epithelial-lined collection of pancreatic secretions.

**Pancreatic pseudocysts are non-epithelial-lined fluid collections that arise as a consequence of acute pancreatitis, trauma, or chronic pancreatitis. They are believed to result from disruption of the pancreatic duct with subsequent leakage of pancreatic exocrine secretions into surrounding peripancreatic tissue. The incidence of pancreatic pseudocysts varies widely, especially with the increased use of axial imaging in patients with pancreatitis and abdominal pain. Most pseudocysts are asymptomatic; the development of symptoms may herald significant complications, including perforation, obstruction, hemorrhage, and infection. Most pseudocysts are single, unilocular lesions. One-third of pseudocysts are located in the pancreatic head and the remainder are found in the body and tail regions. The fluid filling the pseudocyst cavity is usually watery in nature and rich in pancreatic enzymes, including amylase, lipase, and trypsin. Some endoscopic retrograde cholangiopancreatogram studies have shown that in 80% of cases, the pancreatic duct communicates with the pseudocyst.**

## PRESENTATION AND DIAGNOSIS

A lingering course of acute pancreatitis, persistent abdominal pain, or an epigastric mass may be potential indicators of pseudocyst development. Additional signs and symptoms may signify complications. Infection manifests with fever and abdominal pain. Patients with ruptured pseudocysts present with severe acute abdominal pain, peritoneal irritation, and shock. Gastrointestinal bleeding and vomiting occur when pseudocysts erode into the surrounding viscera and vascular structures.

The diagnosis of pseudocysts has been greatly facilitated by the use of axial imaging. Computerized tomography (CT) is the standard for diagnosis and detects small pseudocysts even less than 1 cm in diameter. Moreover, CT is helpful in delineating the features of pseudocysts, including anatomic location, fibrosis of the wall, presence of blood or infectious material, and viability of the surrounding pancreatic parenchyma (Fig. 1).

An assessment of the likelihood of spontaneous resolution and the risk of developing complications guides clinical decision-making. Management may consist of observation and surveillance or intervention. Pancreatic pseudocysts resolve spontaneously through absorption, rupture into neighboring viscus, or drainage through the pancreatic duct, with spontaneous resolution in 50% of cases. Factors that affect the likelihood of spontaneous resolution include size, chronicity, and multiplicity. Most pseudocysts will resolve without intervention within 6 weeks. Lesions that are less than 6 cm in size are more likely to heal than those that are larger than 6 cm. Those attributed to chronic pancreatitis are less likely to heal than pseudocysts secondary to acute pancreatitis. Multilocular lesions

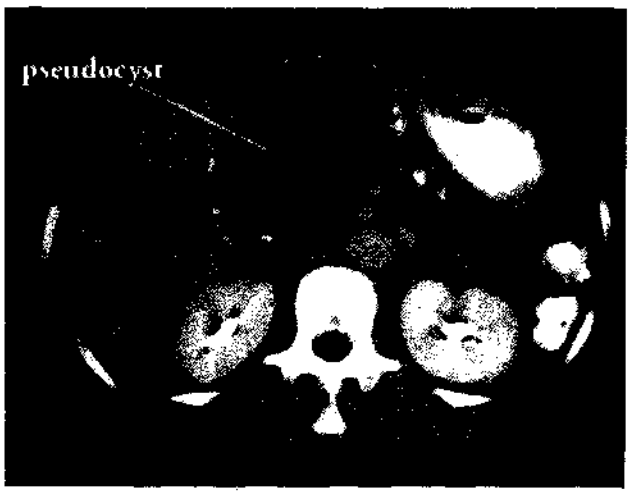


FIGURE 1 CT scan showing a large pancreatic pseudocyst. Reprinted from Guice, K. *In* "Surgery: Scientific Principles and Practice" (L. Greenfield, M. Mulholland, K. Oldham, G. Zelenock, and K. Lillemoe, eds.), 2nd Ed., with permission. Copyright Lippincott-Raven Publishers, 1997.

 

are also less likely to heal spontaneously than unilocular lesions.

## THERAPEUTIC APPROACHES

Endoscopic, percutaneous, and surgical approaches may be employed to treat complicated or symptomatic pancreatic pseudocysts. Endoscopy may be used to create a communication between the pseudocyst and either the stomach or small bowel. A broadly adherent, opposing wall of stomach or small bowel is absolutely required for this approach to be considered; preprocedural axial scanning is required to document this circumstance. A stent or catheter is then deployed, creating a conduit for internal drainage of the pseudocyst. Radiographically guided percutaneous placement of an indwelling catheter into the pseudocyst is another means of treating unresolving or complicated cases of pancreatic pseudocyst. External catheter drainage of the pseudocyst may be complicated by secondary infection of the pseudocyst, catheter obstruction from particulate debris, and the development of enterocutaneous or pancreaticocutaneous fistulas. Surgical approaches to complicated pancreatic pseudocysts are based on creating an internal drainage communication between the pseudocyst and either the stomach or small intestine (Fig. 2). As in the endoscopic approach, a broadly adherent pseudocyst wall is essential to the success of the drainage procedure. Moreover, an adequately mature and fibrous wall is required to ensure a stable anastamosis. Pseudocysts located in the tail of the pancreas may be amenable to resection by distal pancreatectomy. In these cases, splenectomy is warranted if the lesion is in close proximity to the splenic hilum.

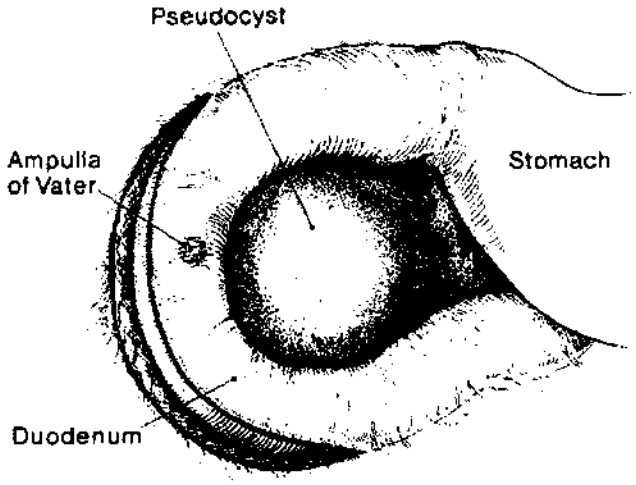


**FIGURE 2** Pancreatic pseudocyst in close apposition to the duodenum, allowing for cyst drainage into the duodenum (cystoduodenostomy). Reprinted from Bradley, E. L. (1997). "Mastery of Surgery" (Nyhus, Baker, Fischer, eds.). 3rd Ed., p. 1228, with permission. Copyright Lippincott Williams & Wilkins.

### See Also the Following Articles

**Exocrine Pancreas • Pancreatic Tumors, Other • Pancreatitis, Acute • Pancreatitis Chronic**

### Further Reading

Cooperman, A. M. (2001). An overview of pancreatic pseudocysts: The emperor's new clothes revisited. *Surg. Clin. North Am.* 81, 391–397.

Guice, K. S. (1997). Acute pancreatitis. *In* "Surgery: Scientific Principles and Practice" (L. Greenfield, M. Mulholland, K. Oldham, G. Zelenock, and K. Lillemoe, eds.), 2nd Ed., pp. 886–887. Lippincott-Raven, Philadelphia.

Yeo, C. J., and Cameron, J. L. (2001). Exocrine pancreas. *In* "Sabiston Textbook of Surgery" (C. Townsend, R. Beauchamp, B. Evers, and K. Mattox, eds.), 16th Ed., pp. 1129–1130. W. B. Saunders Co., Philadelphia, PA.

# Pancreatic Transplantation

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**allograft** A graft transplanted between genetically nonidentical individuals of the same species.

**diabetes mellitus** A chronic metabolic disorder in which utilization of carbohydrate is impaired and that of lipid and protein is enhanced; it is caused by an absolute or relative deficiency of insulin and is characterized, in more severe cases, by chronic hyperglycemia, glycosuria, water and electrolyte loss, ketoacidosis, and coma.

**diabetic neuropathy** A generic term for any diabetes mellitus-related disorder of the peripheral nervous system, autonomic nervous system, and some cranial nerves.

**immunosuppression** Prevention or interference with the development of an immunologic response; it may reflect natural immunologic unresponsiveness (tolerance), may be artificially induced by chemical, biological, or physical agents, or may be caused by disease.

**pancreatic islet** Cellular masses varying from a few cells to hundreds of cells lying in the interstitial tissue of the pancreas that constitute the endocrine portion of the pancreas and are the source of insulin and glucagon.

**renal failure** Loss of kidney function, either acute or chronic, that results in azotemia and syndrome of uremia.

**retinopathy** Retinal changes occurring in diabetes mellitus, marked by microaneurysms, exudates, and hemorrhages, and sometimes by neovascularization.

**Pancreatic transplantation is a surgical treatment for severe diabetes mellitus and its complications. Most commonly, the entire gland is transplanted heterotopically in cases of longstanding type 1 diabetes. In a number of scattered reports, isolated pancreatic islets have been transplanted, with mainly unsatisfactory results. The two primary objectives of pancreatic transplantation are to restore normal glucose homeostasis and to prevent, delay, or reverse the end-organ complications associated with the underlying disease.**

## INTRODUCTION

Pancreatic transplantation has been performed since 1966. Results were poor during the first two decades for three main reasons. First, inability to successfully preserve pancreatic allografts during the required period of time between removal from the donor and implantation into the recipient led to early allograft failure in a significant proportion of cases. Second, fragility of the organ and injury related to ischemia and reperfusion resulted in a high incidence of allograft thrombosis. Third, immunosuppression was inadequate to prevent rejection and the treatment of pancreas transplant rejection was unsatisfactory.

Since the 1980s, results of pancreatic transplantation have steadily improved. Improved procurement techniques and more reliable preservation solutions have reduced the early failure rate and, combined with surgical innovations, have lessened the incidence of early allograft thrombosis. Immunosuppressive drug developments have significantly reduced the incidence, severity, and consequences of allograft rejection and now result in excellent long-term insulin-independent survival.

## INDICATIONS AND CONTRAINDICATIONS

Patients with longstanding type 1 diabetes mellitus are candidates for pancreatic transplantation. A demonstrated absence of C peptide confirms the failure of endogenous insulin production. The development of end-organ complications such as diabetic proliferative retinopathy, peripheral and autonomic neuropathy, gastrointestinal dysmotility, and diabetic nephropathy signals advanced stages of the disease and warrants consideration for transplantation.

Three forms of pancreatic transplantation are offered to suitable patients depending upon the degree of renal impairment. These comprise pancreas transplant alone (PTA), simultaneous pancreas–kidney transplantation (SPK), and sequential pancreas after kidney transplant (PAK).

In patients without marked renal impairment, control of blood glucose via conventional means such as intermittent subcutaneous insulin injections or insulin pump is almost always successful in preventing life-threatening hypoglycemic episodes. However, a small number of patients have severe hypoglycemi

 

unawareness, multiple hospitalizations for diabetic coma or seizures, and inability to control blood sugar despite adequate compliance with an aggressive regimen. These patients may be candidates for PTA, provided that an adequate renal reserve is present.

Individuals who have already developed renal failure are also candidates for pancreatic transplantation and require renal replacement therapy as well, in the form of a kidney transplant. Two modalities are available for such patients and the choice between them depends on the availability of a kidney donor. In the first case, if a living donor is available, the kidney transplant is performed first and the patient may receive a subsequent cadaveric pancreas transplant (PAK), provided that the kidney transplant is functioning adequately. If a living donor transplant is not feasible, the patient may receive both organs from a single cadaveric donor (SPK).

## RECIPIENT EVALUATION

Candidates up to 45 years of age are routinely considered, but older patients require more careful scrutiny due to demonstrated inferior patient and graft survival outcomes. The duration of diabetes mellitus should be assessed and absence of C-peptide secretion confirmed. Systematic assessment of end-organ complications is important. Diabetic retinopathy requiring laser photocoagulation, vitrectomy, or other measures should be assessed. Blindness is not an absolute contraindication to pancreatic transplantation, but its presence may suggest more advanced systemic disease. Peripheral neuropathy and associated musculoskeletal manifestations such as Charcot joints may be present. Autonomic neuropathy with symptomatic orthostatic hypotension and gastrointestinal dysmotility syndromes are common in this patient population. Meticulous investigation of correctable coronary artery disease is mandatory in light of the high incidence of both overt and asymptomatic lesions. The presence of severe peripheral vascular disease is a marker for systemic atherosclerosis and, particularly if associated with major amputation, is considered a relative contraindication. The need for immunosuppressive therapy, with its attendant risks of neoplasia and infection, means that preexisting malignancies (other than nonmelanoma skin cancers) and active or ongoing infections are also contraindications to pancreatic transplantation.

Unlike most surgical procedures, solid organ transplantation requires lifelong immunosuppression and cooperation with a complex medical regimen. Accordingly, patients must be capable of understanding the risks and benefits of the procedure and have a requisite system of social support.

## DONOR CONSIDERATIONS

Virtually all pancreatic transplants are procured from brain-dead cadaveric donors. Donor assessment is a critical step as the pancreas is more susceptible to pre-procurement ischemic injury than other solid organs. Donors over the age of 45 years and those whose cause of death was cerebrovascular accident are risk factors for allograft failure. High levels of vasopressor drugs and the use of antidiuretic drugs (vasopressin, desmopressin) to treat diabetes insipidus in the donor may also be associated with a higher risk of failure.

Most cadaveric pancreata are procured from multiorgan donors from whom kidneys, liver, heart, and lungs are also being retrieved. Coordination between several donor operative teams may therefore be necessary, although these procedures are now fairly standardized. The entire pancreas along with the associated donor duodenum is procured. The vascular anatomy of the liver and pancreas must be shared, since the portal vein is the venous outflow for the pancreatic allograft and is also required for the liver. Similarly, the arterial blood supply to the pancreas and liver arises from the celiac axis and arterial anomalies, which may be found in upward of 20% of donors, must be assiduously searched for and preserved.

## RECIPIENT OPERATION

Technical details of the recipient pancreas transplant have evolved significantly. Placement of the organ into the iliac fossa within the peritoneal cavity (as opposed to the retroperitoneum) is preferred. Arterial blood supply to the pancreas, arising from branches of the celiac axis and from the superior mesenteric artery, dictate *ex vivo* reconstruction prior to implantation. A Y-graft of bifurcated donor iliac artery is generally used to enable a single arterial anastomosis to the common or external iliac artery in the recipient. The donor portal vein is anastomosed to the external iliac vein of the recipient.

The more common systemic drainage results in chronic hyperinsulinemia, although no specific adverse consequences have emerged and glucose homeostasis is excellent. Some groups have advocated portal venous drainage of the pancreas as a more physiological setup. First passage of pancreatic venous blood through the liver is associated with normal levels of circulating

insulin and a glucose tolerance that more closely approximates a normal pattern.

Exocrine secretion of the pancreas is the Achilles heel of pancreatic transplantation. The two major choices are to create an anastomosis between the donor duodenum and the recipient bladder or to create an anastomosis between the donor duodenum and the recipient small bowel. The former was used for many years, as it was perceived to be safer in the event of a postoperative leak. However, dehydration and acidosis from urinary losses of alkaline pancreatic secretions have led to a return to enteric drainage of the donor pancreas in over one-half of cases.

The pancreas allograft is placed contralateral to a kidney transplant. Most groups prefer to place the pancreas graft on the right side if possible. Since the left iliac vein passes under the iliac artery on that side, placement of the pancreas on the left may result in venous hypertension in the graft and a higher risk of allograft thrombosis.

## IMMUNOSUPPRESSION

The majority of transplant centers use anti-lymphocyte preparations as part of an induction immunosuppression regimen following pancreatic transplantation. The agents available include polyclonal (equine and rabbit) and murine monoclonal antibodies to the T-cell CD3 receptor or the receptor for interleukin-2. Maintenance immunosuppression usually consists of a three-drug cocktail using a calcineurin inhibitor (cyclosporine or tacrolimus), an anti-metabolite (usually mycophenolate mofetil), and corticosteroids.

Rejection occurs in up to one-half of recipients. It must be diagnosed early and treated aggressively to avoid graft failure. The diagnosis increasingly relies on a tissue biopsy obtained percutaneously, laparoscopically, or via laparotomy. Pancreas allograft rejection is most commonly treated with a full course of anti-lymphocyte globulin or monoclonal anti-T-cell antibody.

## OUTCOME

The success of pancreatic transplantation can be measured in terms of patient and graft survival as well as by the effects of the transplant on end-organ complications. Patient survival for all modalities of the procedure (PTA, SPK, PAK) exceeds 94% at 1 year and 83% at 5 years. Pancreas graft survival rates are dependent on several factors, the most important of which is the modality of therapy (Table I). SPK recipients have the highest pancreas graft survival rates, closely followed by recipients of PAK transplants. Rejection is easiest to diagnose in SPK recipients, where the kidney transplanted from the same cadaveric donor acts as a barometer for the immunologic response to the grafts. Those who receive a PTA have the poorest results, presumably because the diagnosis of rejection is more difficult.

**TABLE I** 1- and 3-Year Pancreas Transplant Graft Survival Rates by Modality of Transplantation

| Pancreas transplant modality | 1-year graft survival (%) | 3-year graft survival (%) |
|---|---|---|
| Simultaneous pancreas–kidney transplant | 84 | 77 |
| Pancreas after kidney transplant | 70 | 56 |
| Pancreas transplant alone | 64 | 50 |

Diabetic retinopathy may paradoxically worsen transiently after pancreatic transplantation, but by 2 years post-SPK transplantation a higher proportion of patients have stable eyes when compared to comparable diabetic patients treated with kidney transplant alone. Peripheral neuropathy may have multifactorial etiology, particularly in patients with established renal failure. Nevertheless, pancreas transplant recipients have been shown to have less severe and more slowly progressive neuropathy than their nontransplanted counterparts. A successful pancreatic transplant protects the transplanted kidney (or the native kidney in the case of a PTA) from the development or progression of diabetic nephropathy.

Quality of life is dramatically improved for recipients of pancreatic transplantation. Freedom from decades of dietary restrictions and abolition of the fear of hypoglycemic coma or seizures are obvious benefits. Objective measures of health status and quality of life have been repeatedly demonstrated to be greatly improved among pancreatic transplant recipients.

## STATUS OF ISLET TRANSPLANTATION

Since the primary objective of pancreatic transplantation is the restoration of glucose homeostasis, the concept of isolated pancreatic islet transplantation has been attractive for many years. Unfortunately, despite several decades of research and modest numbers of human clinical investigations, long-term insulin independence has been achieved in fewer than 10% of cases. A recent effort using a corticosteroid-free immunosuppressive regimen in a small number of patients has provided promising results. Improved methods for large-scale islet isolation and more effective immunosuppressive drugs are

credited with these successes. However, long-term follow-up will be required before any conclusions can be drawn regarding the efficacy of this approach.

### See Also the Following Articles

**Diabetes Mellitus • Diabetic Neuropathies • Endocrine Pancreas • Exocrine Pancreas • Transplantation Immunology**

### Further Reading

Gruessner, A. C., and Sutherland, D. E. (2000). Pancreas transplant outcomes for United States (US) cases reported to the United Network for Organ Sharing (UNOS) and non-US cases reported to the International Pancreas Transplant Registry (IPTR) as of October, 2000. *Clin. Transplant.*, 45–72.

Hricik, D. E. (2000). Kidney–pancreas transplantation for diabetic nephropathy. *Semin. Nephrol.* 20, 188–198.

Ojo, A. O., Meier-Kriesche, H. U., Hanson, J. A., *et al.* (2001). The impact of simultaneous pancreas–kidney transplantation on long-term patient survival. *Transplantation* 71, 82–90.

Robertson, R. P., Davis, C., Larsen, J., Stratta, R., and Sutherland, D. E. (2000). Pancreas and islet transplantation for patients with diabetes. *Diabetes Care* 23, 112–116.

Rosenberg, L. (1998). Clinical islet cell transplantation: Are we there yet? *Int. J. Pancreatol* 24, 145–168.

Shapiro, A. M., Lakey, J. R., Ryan, E. A., *et al.* (2000). Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. *N. Engl. J. Med.* 343, 230–238.

Sutherland, D. E., Gruessner, R. W., Dunn, D. L., *et al.* (2001). Lessons learned from more than 1,000 pancreas transplants at a single institution. *Ann. Surg.* 233, 463–501.

Sutherland, D. E., Gruessner, R. W., and Gruessner, A. C. (2001). Pancreas transplantation for treatment of diabetes mellitus. *World J. Surg.* 25, 487–496.

# Pancreatic Triglyceride Lipase

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**dietary fats** Predominantly triglycerides, which consist of acyl chains or fatty acids linked to glycerol through ester bonds.

**lipase** Enzyme that catalyzes the hydrolysis of ester bonds in dietary fats to release fatty acids.

**pancreatic triglyceride lipase** Specific enzyme produced and secreted by pancreatic acinar cells; primarily responsible for intestinal digestion of triglycerides.

**Pancreatic triglyceride lipase is the major pancreatic lipase synthesized and secreted by pancreatic acinar cells. It accounts for most of the luminal digestion of triglycerides in the small intestine. This function is critical for the utilization of dietary triglycerides, because intestinal enterocytes cannot absorb long-chain triglycerides unless lipases convert them to fatty acids and monoacylglycerols.**

## INTRODUCTION

The digestion of dietary fats in humans begins in the stomach, where gastric lipase (a distinct protein) releases about 15% of the fatty acids from triglycerides. Lipases secreted by the pancreas complete dietary fat digestion in the small intestine. Of these lipases, pancreatic triglyceride lipase (PTL) predominates, as evidenced by patients with congenital deficiency of PTL who malabsorb 50–60% of dietary fats. Cholesterol esterase, another nonspecific lipase, mediates the hydrolysis of other dietary lipids. Other more distantly related lipases, such as lipoprotein lipase and hormone-sensitive lipase, mediate the uptake and release of fatty acids from various tissues.

## PHYSIOLOGY

Only the pancreas synthesizes significant amounts of PTL, and this occurs in the acinar cells of the pancreas. In addition to this tissue-specific expression, mRNA encoding PTL shows temporal and cell-specific regulation. The fetal pancreas of humans and rodents does not express mRNA for PTL. After birth, the pancreas of suckling mouse or rat pups does not express PTL mRNA until the suckling–weanling transition.

Human newborns have decreased lipase activity in pancreatic secretions and may also have decreased expression of PTL. Once expressed, mRNA encoding PTL appears in the pancreatic acinar cells and not in other cell types in the pancreas. Pancreatic acinar cells synthesize and secrete PTL into the pancreatic duct through both basal and regulated pathways. In the common duct, PTL mixes with biliary lipids and bile salts before entering the duodenum, where lipolysis occurs. PTL is active at the neutral pH normally present in the intestinal lumen. It can be inactivated by low pH, as occurs with gastric hypersecretion.

## LIPOLYSIS

PTL is a carboxyl esterase that prefers acylglycerides to other dietary lipids, such as phospholipids, cholesterol esters, and galactolipids. PTL efficiently hydrolyzes a broad range of acyl chains of varying length and saturation from the 1 and 3 positions of tri- and diglycerides, producing fatty acids and 2-monoacylglycerides. *In vitro*, PTL cleaves acyl chains from $C_{14}$ to $C_{22}$ carbon chains with only a sixfold difference in rates between the best and worst substrates.

Several properties of PTL distinguish it from other enzymes. Like all lipases, PTL has low activity against water-soluble substrates and has much higher activity against water-insoluble substrates at oil–water interfaces, such as those presented by emulsions of dietary lipids. Paradoxically, many of the usual constituents of the duodenum, such as bile salts, phospholipids, proteins, and polysaccharides, inhibit PTL. Another pancreatic protein, colipase, restores activity to PTL under these conditions by anchoring it at the lipid–water interface.

## PROTEIN STRUCTURE

The primary structures of PTL and of colipase from multiple species have been solved by chemical methods or predicted from their cDNA sequence. Both proteins are synthesized with 17-amino-acid signal peptides. Mature human PTL contains 449 amino acids (molecular mass, 49,558 Da) and human colipase contains 95 amino acids (molecular mass, 10,104 Da). In contrast to many other pancreatic exocrine proteins, PTL is not synthesized as an inactive proform or zymogen. Colipase is secreted as a proform, called procolipase, that contains a five-amino-acid propiece, which is cleaved to produce colipase. Unlike the exocrine proenzymes, procolipase does function and can restore activity to bile-salt-inhibited PTL.

The three-dimensional structure of PTL without colipase and two structures of the PTL–colipase complex have greatly increased our understanding of PTL function. PTL consists of two distinct domains, an N-terminal $\alpha/\beta$ hydrolase fold and a C-terminal $\beta$-sheet structure with homology to the C2 domains that are found in a wide range of proteins. Colipase binds to the C-terminal domain of PTL. The active site of PTL resides in the N-terminal domain and contains a glutamic acid–histidine–serine catalytic site. In the PTL structure and in one of the PTL–colipase structures, a surface loop covers the active site and prevents substrate from entering the active site. In the other PTL–colipase structure, the "lid" has moved into a position that opens and configures the active site and, together with colipase, presents a large hydrophobic surface that serves as the lipid binding site.

### See Also the Following Articles

**Amylase • Fat Digestion and Absorption • Pancreatic Digestive Enzymes • Pancreatic Enzyme Secretion (Physiology) • Trypsin**

### Further Reading

Brockman, H. (2001). Pancreatic lipase: Physiological studies. *In* "Intestinal Lipid Metabolism" (C. Mansbach II, P. Tso, and A. Kukis, eds.), pp. 37–54. Kluwer Academic/Plenum Pub., New York.

Lowe, M. (2001). Molecular mechanisms of pancreatic lipase and colipase. *In* "Intestinal Lipid Metabolism" (C. Mansbach I, P. Tso, and A. Kukis, eds.), pp. 37–54. Kluwer Academic/Plenum Publ., New York.

# Pancreatic Tumors, Other

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**pancreatic cystic neoplasms** Pancreatic tumors that arise from parenchymal cells and often form cystic shapes seen in imaging studies.

**pseudocyst** A non-epithelial-lined collection of pancreatic secretions.

**The vast majority of pancreatic tumors are adenocarcinomas arising from the ductal epithelium. Pancreatic tumors other than ductal adenocarcinoma are rare and can be broadly classified as cystic versus solid lesions. The primary cystic neoplasms of the pancreas represent the majority of these tumors; other rare solid tumors are occasionally seen.**

## INTRODUCTION AND CLASSIFICATION

Lesions arising from within the pancreas can generally be classified as either cystic or solid and as benign or malignant. However, the distinction between benign and malignant neoplasms can be difficult to make and several tumors represent a spectrum of disease with an indistinct transition point from benign to malignant. The most commonly encountered masses in the pancreas are not tumors or cysts but collections of fluid with a fibrous wall, termed pseudocysts. Pancreatic adenocarcinoma represents the most common neoplasm of the pancreas, accounting for perhaps 90–95% of tumors. The other tumors are all considered rare and can be classified based on appearance as cystic or solid (see Table I). The solid tumors include nonendocrine tumors, metastatic cancers, and endocrine tumors. This article will focus on the primary cystic neoplasms of the pancreas with a brief discussion of the assortment of other solid nonendocrine tumors.

TABLE I Classification of Pancreatic Tumors

- A. Cystic
  - a. Mucinous cystic neoplasms
    - i. Mucinous cystadenoma
    - ii. Mucinous cystic tumor with moderate dysplasia
    - iii. Mucinous cystadenocarcinoma
  - b. Serous cystadenoma
  - c. Serous cystadenocarcinoma (case reports)
  - d. Intraductal papillary mucinous tumor
  - e. Acinar cell cystadenocarcinoma
  - f. Cystic choriocarcinoma
  - g. Cystic teratoma
  - h. Cystic islet cell tumor
  - i. Cytic necrosis of adenocarcinoma/lymphoma
  - j. Papillary cystic epithelial neoplasm
  - k. Angimatous neoplasms
    - i. Angioma
    - ii. Lymphangioma
    - iii. Hemangioendothelioma
- B. Solid
  - a. Ductal adenocarcinoma
  - b. Pancreatic lymphoma (primary vs systemic)
  - c. Adenosquamous carcinoma
  - d. Giant cell carcinoma (sarcomatoid or osteoclast-like carcinoma)
  - e. Acinar cell carcinoma
  - f. Pancreaticoblastoma

### Cystic Tumors of the Pancreas

The cystic neoplasms were first recognized in 1824 but their classification has continued to evolve for the past 180 years. Initially, cystic tumors were recognized according to the sizes of the cysts, being either microcystic or macrocystic. In 1978, the distinction between two major types of cystic neoplasms was made according to the nature of the cyst contents: serous versus mucinous. A few years later in 1982, the third major tumor in this class was discovered. However, the terminology varied considerably and not until the late 1990s was the term intraductal papillary mucinous tumor (IPMT) widely accepted.

The list of cystic tumors within the pancreas is large but more than 90% of these tumors are composed of mucinous cystic neoplasms, serous cystadenomas, and IPMTs. The remainder are exceedingly rare and limited information is available regarding their nature. These tumors have many similar features in age of onset, clinical presentation, and treatment; however, prognosis varies considerably. The most important differential diagnosis to consider with all cystic tumors is the vastly more common pseudocyst for which detailed historical

 

information regarding pancreatitis or abdominal trauma is paramount. Other findings to suggest pseudocyst rather than cystic tumor include lack of septations, loculations, solid components, or calcifications on computed tomography (CT) or any communication between the cyst and ductal system on endoscopic retrograde cholangiopancreatography (ERCP). Perhaps the best distinguishing feature is the amylase content of the aspirated fluid, generally greater than 5000 IU/liter.

### *Mucinous Cystic Neoplasms*

These tumors represent a spectrum of disease ranging from presumably benign to clearly malignant with local invasion and distant metastases occasionally seen. Previously classified as mucinous cystadenoma with variable degrees of dysplasia versus cystadenocarcinoma, the currently favored term is mucinous cystic neoplasms (MCNs) due to the difficulty in accurately diagnosing these lesions as benign versus malignant.

The MCNs are the most frequently encountered form of cystic neoplasm in the pancreas, representing 45–50% of these tumors. Women are more commonly affected, perhaps as high as 4:1, and the median age at diagnosis is 50–55 years. MCNs are usually composed of multiple cysts and range in size from 1 to 26 cm. Benign tumors tend to be smaller (5 to 6 cm), whereas malignant tumors average 8 to 11 cm. The mucinous tumors tend to be "macrocystic" in appearance, with fewer cysts and each cyst greater than 2 cm in size. Solid components and calcifications are occasionally found and usually connote a malignant change. The majority of MCNs are found in the body and tail of the pancreas and rarely connect with the ductal system (5%).

The majority of patients diagnosed with MCNs are symptomatic. Common presenting symptoms include vague abdominal pain, bloating or abdominal fullness, and early satiety. A few patients are able to feel an abdominal mass. Jaundice, pancreatitis, and weight loss are less common to rare. An increasing percentage of patients are asymptomatic and found to have incidental pancreatic masses after abdominal imaging for unrelated conditions. Diagnosis is then made after abdominal imaging is obtained, with ultrasound (US), CT, or magnetic resonance imaging. Although MCNs can be suspected based upon radiologic findings, a definitive diagnosis requires either aspiration of cyst fluid or surgical resection. Large tumors can be percutaneously aspirated safely; however, smaller tumors are increasingly being sampled via endoscopic US (EUS). Characteristic and diagnostic features of MCN fluid include high viscosity, positive mucin staining, low amylase, positive cytology (in 50%), and moderately elevated carcinoembryonic antigen (CEA) >200 ng/ml.

The lining of MCNs is composed of a mucin-producing tall columnar epithelium with a ductal origin. Up to 75% of cysts have been found to have regions of cyst wall denuded of epithelium, involving on average 40% of the wall. In addition, multiple reports of benign, dysplastic, and malignant epithelium coexisting within the same tumor have been described. For these reasons, once an MCN is suspected, surgical resection is strongly advised. This should entail either a distal pancreatectomy with splenectomy or a pancreaticoduodenectomy or Whipple procedure. Limited enucleation is not recommended. Long-term survival is good for patients with resectable disease, ranging from 50 to 75% at 5 years. Studies of adjuvant therapy including chemotherapy and radiation are ongoing and thus their effectiveness is not fully known.

### *Serous Cystadenoma*

As opposed to its mucinous counterpart, the serous cystic tumor represents a more homogenous and predictable entity. Almost universally benign, only six case reports of malignant serous cystadenocarcinomas have been reported.

The serous cystadenomas are probably the second most common cystic tumor of the pancreas, representing 16 to 27% of cystic tumors in most series. Similar to MCNs, women are predominantly affected, again approaching 4:1 in incidence, and age at diagnosis is typically the sixth or seventh decade. These tumors can also be a component in 15% of patients with Von Hippel-Lindau syndrome. Concomitant renal, retinal, or cerebellar vascular tumors are usually found. The overall size of the serous tumors is similar to MCNs at 1 to 26 cm with an average of 6 to 10 cm, but the individual cysts tend to be much smaller, ranging from micrometers to 2 cm in diameter in a honeycomb fashion. The previously descriptive classification of "microcystic" adenoma is no longer used. Unlike the MCNs, serous tumors often have characteristic findings on radiologic imaging. The vascular, fibrous, calcified connective tissue of the tumor creates a central stellate scar with a characteristic "sunburst" pattern on plain films, CT, or angiography. Unfortunately, this pathognomonic finding is present in only 10 to 30% of tumors. Some authors believe that if it is present, further diagnostic testing, such as cyst aspiration, is unnecessary. Although found throughout the gland, these tumors tend to occur in the head of the pancreas more commonly than MCNs.

As with MCNs, the majority of patients diagnosed with serous tumors are symptomatic at presentation.

Symptoms are generally related to mass effect and include abdominal pain, fullness, and the feeling of a mass in up to 33% of patients. Biliary or pancreatic obstruction resulting in jaundice, cholangitis, or pancreatitis is unusual. Weight loss may be present, probably related to early satiety rather than to anorexia as is commonly found with malignancy. The proportion of patients who are asymptomatic at diagnosis will likely continue to increase with the rising use of abdominal imaging modalities for various complaints. As with MCNs, definitive diagnosis of serous cystadenomas usually requires additional testing after initial radiographic studies reveal a cystic mass. Aspiration of cyst fluid is helpful but may be more difficult due to smaller sizes of the individual cysts. The fluid can usually be distinguished from MCNs or pseudocysts by finding low viscosity, negative mucin staining, low CEA $< 5$ ng/ml, low amylase, and a unique characteristic of positive PAS (periodic acid-Schiff)-staining cells on cytologic analysis due to the abundant glycogen. PAS-positive cells are reported in approximately half of cases and if present, strongly support the diagnosis.

The epithelium of serous cystadenomas is composed of glycogen-rich low cuboidal cells. No mucin is produced. Unlike the MCNs, the progenitor cell is believed to be the centroacinar cell as opposed to ductal epithelial cells. The problem of frequently coexisting benign and dysplastic cells has not been reported for serous tumors. Due to the more benign nature of these tumors, patient management includes more options. Patients who are elderly or otherwise poor surgical candidates and asymptomatic patients may be safely followed with surveillance imaging. If the lesion continues to grow or symptoms develop or worsen, then surgical referral can be reconsidered. Most authors agree that young patients or symptomatic patients should undergo complete resection with either a distal pancreatectomy or a Whipple procedure to eliminate the chance of malignant degeneration as well as potential complications, such as hemorrhage or obstruction. Long-term survival is excellent.

### *Intraductal Papillary Mucinous Tumor*

In the early 1980s, a new subset of the mucinous cystic tumor was noted that tended to involve the ductal system causing ductal dilation as well as acute and chronic pancreatitis. Various names were given to describe this subset of tumors, such as mucinous ductal ectasia, mucin-hypersecreting tumor, mucinous villous adenomatosis, and ductectatic mucinous cystadenoma, to name a few. By the mid-1990s, the consensus was for intraductal papillary mucinous tumor (IPMT). Similar to MCNs, IPMTs encompass a spectrum of disease from entirely benign to frankly malignant with many intermediates in between. Approximately 40% of tumors are malignant at time of presentation.

IPMTs are less common than MCNs, but are similar in incidence to serous tumors, representing the third most common cystic tumor of the pancreas (some authorities list IPMT as the second most common type). The incidence has risen over the past decade, likely due to increasing recognition of this distinct tumor type as well as improved radiographic techniques. Unlike both MCNs and serous tumors, males are more commonly affected with IPMTs. Age of onset is usually over 60 years. The gross and histologic findings are distinct from the other cystic tumors in that there is a papillary growth of tumor within the main or secondary pancreatic ducts, giving rise to main duct or branch duct types. The ducts then become obstructed and subsequently dilated, giving the appearance of a cystic tumor. "Mucin lakes" have been described in the surrounding pancreas and one series reported 20% to have concomitant lesions similar to MCNs, typically in the head of the pancreas. These likely represent the branch duct type with cystic dilations. The other characteristic finding, usually seen at ERCP, is protrusion of the major and/or minor papillae into the duodenum with extrusion of copious amounts of mucin.

As with the other cystic tumors of the pancreas, the majority of patients with IPMT are symptomatic at diagnosis. Unlike other cystic tumors, patients with IPMT frequently suffer from recurrent acute pancreatitis or chronic pancreatitis with episodic or chronic abdominal pain and symptoms related to obstruction of the bile ducts, pancreatic ducts, or small bowel. Weight loss, steatorrhea, and diabetes are not uncommon. Elevations of amylase or lipase are found in up to half of patients at presentation. The tumor markers CEA and CA19-9 are elevated in approximately 10 to 15% but are not felt to be useful in diagnosis due to the low specificity. Diagnosis usually requires advanced endoscopic techniques such as ERCP and EUS with fine-needle aspiration. Characteristic findings include a patulous ampulla with mucus emanating from a dilated orifice, cystic dilation of the main and secondary ducts, filling defects within the ducts, and pancreatic parenchymal atrophy. Strictures are notably absent. ERCP also allows for collection of ductal secretions and forceps biopsy for pathology and cytology. EUS is particularly helpful in distinguishing this tumor from chronic pancreatitis, which can have a similar appearance. These procedures are important for outlining the extent of disease to plan for surgical resection.

The epithelium of the IPMTs is composed of tall columnar mucin-producing cells, similar to MCNs.

These cells tend to form papillary projections, which can also be seen in MCNs. The epithelium frequently undergoes hyperplastic, dysplastic, and carcinomatous changes. Local invasion is not uncommon. The disease typically begins in the head of the pancreas with slow spread throughout the gland. Due to the high likelihood of finding malignant disease at diagnosis or on follow-up, complete resection is strongly recommended for all surgical candidates without evidence of local or metastatic spread. This typically requires a pancreaticoduodenectomy, distal pancreatectomy with splenectomy, or total pancreatectomy. The use of intraoperative frozen sections to outline the extent of malignancy is essential for curative resections. The survival for patients with curative resections is good, with estimates of 60 to 80% at 5 years. Patients with unresectable disease have outcomes similar to those for pancreatic adenocarcinoma.

### *Other Cystic Lesions*

The vast majority of cyst-like lesions within the pancreas are not true cysts or tumors but actually pseudocysts. These are collections of pancreatic secretions related to ductal disruption after acute pancreatitis or pancreatic trauma.

Other cysts within the pancreas are exceedingly rare. These can be classified as congenital/inherited, infectious, and neoplastic. The congenital/inherited lesions include simple cysts, polycystic disease (with or without kidney involvement), Von Hippel-Lindau disease, dermoid cysts, and macrocysts secondary to cystic fibrosis. Infections with parasites such as *Echinococcus granulosis* and *Taenia solium* can also produce cystic lesions within the pancreas. Other neoplastic cystic lesions in addition to the three most common ones described above include acinar cell cystadenocarcinoma, cystic choriocarcinoma, cystic teratoma, cystic islet cell tumors/acinar cell cystadenocarcinoma (usually nonfunctioning), cystic necrosis of adenocarcinoma or lymphoma, papillary cystic epithelial neoplasms, and angiomatous lesions, such as angiomas, lymphangiomas, and hemangioendotheliomas. These tumors are described in the literature with case reports, and only minimal details regarding their clinical behavior are known.

## Solid Tumors of the Pancreas

Though the overwhelming majority of solid tumors in the pancreas are adenocarcinomas, a few other types of tumors are known to occur and will be described here.

Lymphomas can involve the pancreas in up to one-third of patients. However, primary lymphoma of the pancreas is a rare tumor, accounting for less than 1% of all extranodal non-Hodgkin's lymphomas and only 0.3% of pancreatic tumors. Abdominal pain and weight loss are common complaints at presentation. Lactate dehydrogenase may be elevated. Due to the large size attained by these tumors, a palpable mass can be felt in over half of patients. Jaundice may be found in one-third. Pancreatitis is uncommon. These tumors are frequently misdiagnosed as adenocarcinoma prior to surgery. A clue to the diagnosis may be an unusually large solid tumor. Therapy consists of combination chemotherapy and radiation but survival is poor.

Two variants of ductal adenocarcinoma include adenosquamous carcinoma and giant cell carcinoma of the pancreas. Both arise from the ductal cell. Adenosquamous cancers have a transition point to squamous epithelium. They tend to be hypervascular. The giant cell carcinoma is also known as sarcomatoid and several subtypes have been described. Of note, these tumors tend to spread hematogenously and generate distant metastases unlike adenocarcinoma. Overall, the clinical presentation, response to therapy, and prognosis are very similar to those for adenocarcinomas.

Acinar cell carcinomas have also been described. These malignant tumors arising from the endocrine portion of the pancreas can present as cystic or solid tumors. Most are nonfunctioning and are discovered incidentally or due to mass effect. Serum lipase levels may be elevated and peripheral fat necrosis may be noted.

Pancreaticoblastoma is a rare tumor usually found in children at a mean age of 4 years. Girls are affected more often than boys. Rare cases can present in adulthood. The tumors tend to be large at the time of presentation and symptoms of pain or fullness are related to mass effect. Distant metastases can develop. Treatment involves wide excision.

## See Also the Following Articles

**Pancreatic Ductal Adenocarcinoma • Pancreatic Pseudocysis**

## Further Reading

Farrell, J., and Brugge, W. (2002). Intraductal papillary mucinous tumor of the pancreas. *Gastrointest. Endosc.* 55, 701–714.

Fernandez-del Castillo, C., and Jimenez, R. (2002). Pancreatic cancer, cystic pancreatic neoplasms, and other nonendocrine pancreatic tumors. *In* "Sleisenger and Fordtran's Gastrointestinal and Liver Disease" (M. Feldman, L. Friedman, and M. Sleisenger, eds.), 7th Ed., pp. 970–987. W. B. Saunders, Philadelphia, PA.

Goldschmiedt, M., and Gutta, K. (1998). Other tumors and diseases of the pancreas. *In* "Sleisenger and Fordtran's Gastrointestinal and Liver Disease" (M. Feldman, L. Friedman, and M. Sleisenger, eds.), 6th Ed., pp. 895–901. W. B. Saunders, Philadelphia, PA.

Kimmey, M. (2002). Cystic neoplasms of the pancreas. *In* "The American College of Gastroenterology 2002 Postgraduate Course" (P. McNally and G. Zuccaro, eds.), pp. 481–488. American College of Gastroenterology, Arlington, VA.

Saur, M., and Yeo, C. (1994). Cystic and pseudocystic diseases of the pancreas. *Curr. Prob. Surg.* **31**, 167–243.

# Pancreatitis, Acute

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**computed tomography scan** Radiographic technique allowing visualization by computer reconstruction of a plane or section through the body.

**endoscopic retrograde cholangiopancreatography** Procedure whereby the pancreatic ducts are visualized by endoscopic injection of contrast media.

**pancreatic pseudocyst** Non-epithelial-lined collection of pancreatic secretions.

**pancreatitis** Inflammatory disease of the pancreas.

**serum amylase** Pancreatic amylase in the serum; serves as a marker of acinar cell damage, i.e., pancreatitis.

**trypsin activation peptide** Part of the molecule cleaved from trypsinogen to activate trypsin.

**zymogens** Proteolytic proenzymes that exist in cells as an inactive precursor; pancreatic zymogens are normally activated by cleavage in the gut lumen.

**Pancreatitis is an inflammatory disease of the pancreas. In clinical terms, acute pancreatitis usually develops rapidly and without a prior history of repeated pancreatitis attacks. In contrast, chronic pancreatitis may be characterized by symptoms that slowly develop and a history of multiple previous pancreatitis attacks. Pathologically, acute pancreatitis is defined as pancreatitis that occurs in a previously healthy gland and that, after the acute attack resolves, leaves a pancreas that may be both morphologically and functionally normal. In contrast, the gland is usually abnormal before an attack of chronic pancreatitis becomes clinically apparent. That preexisting abnormality usually involves diffuse fibrosis of the gland with loss of both exocrine and endocrine elements, and those changes persist even after the attack of chronic pancreatitis has resolved.**

## PATHOLOGY

An attack of acute pancreatitis may be either mild or severe. Pathological changes of mild acute pancreatitis include edema, peripancreatic fat necrosis, and a mild intrapancreatic inflammatory reaction. In contrast, severe pancreatitis is pathologically characterized by varying degrees of parenchymal necrosis along with a severe intrapancreatic inflammatory reaction. Intrapancreatic hemorrhage as well as both intrapancreatic and peripancreatic fluid collections can be seen in severe pancreatitis along with extensive peripancreatic fat necrosis.

## ETIOLOGY

Acute pancreatitis typically occurs as a consequence of some other process; collectively, those processes are referred to as the "etiologies" of acute pancreatitis. In developed countries, roughly 80% of patients with acute pancreatitis develop their disease as a result of either biliary tract stone disease or as a result of prolonged and excessive abuse of ethanol. In any particular population, the distribution between these two causes is related to the incidence of those inciting events in that population—i.e., in inner city populations, ethanol abuse is the most common cause, whereas in more affluent suburban groups, biliary tract stones account for most cases of pancreatitis. A number of drugs can also cause pancreatitis (see Table I). Duodenal or pancreatic tumors as well as other lesions causing pancreatic duct

TABLE 1 Drugs That May Cause Acute Pancreatitis

| Definite causes | Probable causes | Equivocal causes |
|---|---|---|
| Furosemide | L-Asparaginase | Rifampin |
| Valproic acid | Phenformin | H2 blockers |
| Azathioprine | Acetominophen | Isoniazid |
| 6-Mercaptopurine | Procainamide | Steroids |
| Methyl-DOPA | Chlorthalidone | Acetaminophen |
| Tetracycline | Erythromycin | Propoxyphene |
| Ethycrynic acid | Iatrogenic hypercalcemia | |
| Sulfonamides | | |
| Metronidazole | | |
| 5-Aminosalicylate | | |
| Pentamidine | | |
| Estrogens | | |
| Dideoxyinosine | | |
| Thiazides | | |

obstruction (e.g., duodenal Crohn's disease, duodenal ulcers, or periampullary diverticulitis) can also precipitate an attack of acute pancreatitis. Some patients have acute pancreatitis on a hereditary basis. Recent studies have identified a number of genetic mutations that are associated with pancreatitis in those individuals. In some people, the mutation results in an abnormal cationic trypsinogen that, once activated, may be resistant to inactivation by trypsin inhibitors in the pancreas. In other individuals, hereditary pancreatitis may be due to genetic defects that result in production of ineffective trypsin inhibitors in the pancreas. Pancreatitis can also be triggered by a number of miscellaneous events, including hyperlipidemia, shock, hypothermia, trauma, scorpion bites, and endoscopic retrograde cholangiopancreatography (ERCP). The anatomic variant pancreas divisum has also been associated with episodes of pancreatitis, but whether it should be considered a cause of acute pancreatitis is a controversial issue. Roughly 15% of patients develop pancreatitis for no identifiable reason. In those cases, the pancreatitis is considered to be "idiopathic." Recent reports have suggested that many of those patients with idiopathic pancreatitis actually have pancreatitis as a result of overlooked biliary tract disease (microlithiasis), an autoimmune process, or cystic fibrosis.

The mechanisms by which a biliary tract stone might trigger acute pancreatitis have been the subject of considerable study and speculation. Opie suggested in 1901 that a stone might migrate into or through the terminal biliopancreatic ductal system, causing obstruction and creating, behind that obstruction, a common bile–pancreatic channel that would permit bile to reflux, retrogradely, into the pancreatic duct. More recent studies, however, have indicated that stone-induced obstruction of the pancreatic duct, rather than reflux of bile into the pancreatic duct, is the event that probably triggers acute pancreatitis. Presumably, the stone, or inflammation caused by passage of a stone, causes obstruction of the distal duct, and continued secretion above that obstruction leads to pancreatic ductal hypertension. By mechanisms that have not been defined, pancreatic ductal hypertension then causes changes within pancreatic acinar cells that result in acinar cell injury and pancreatitis (see below).

The mechanisms by which ethanol abuse might cause acute pancreatitis are not known with certainty, but it is generally believed that ethanol or one of its metabolites triggers pancreatitis by exerting a direct toxic effect on the pancreas, much like a drug. Experimental evidence to support this hypothesis is, however, limited. The chronic pancreatitis that is associated with prolonged and excessive ethanol abuse may reflect changes resulting from repeated subclinical episodes of acute ethanol-induced pancreatitis.

## PATHOPHYSIOLOGY

The earliest changes of acute pancreatitis appear to occur within pancreatic acinar cells, and perhaps the earliest of those changes involves intraacinar cell activation of digestive enzyme zymogens. The pancreatic acinar cell synthesizes and secretes a large number and amount of digestive enzymes, and those enzymes play a critical role in digestion. Under normal conditions, the potentially harmful digestive enzymes are synthesized and secreted as inactive proenzymes or zymogens, which become activated only after they traverse the pancreatic ductal system and enter the duodenum. There, the brush border enzyme enterokinase (enteropeptidase) catalyzes the activation of trypsinogen and trypsin activates the other zymogens, including chymotrypsinogen, proelastase, and the procarboxypeptidases. During the earliest stages of pancreatitis, activation of digestive enzyme zymogens, including trypsinogen, occurs within acinar cells. The mechanisms responsible for that intraacinar cell activation of trypsinogen are not entirely clear, but one widely accepted hypothesis suggests that it is catalyzed by lysosomal hydrolases such as cathepsin B and that the activation occurs because lysosomal hydrolases and digestive enzymes become colocalized within membrane-bounded intracellular organelles during the very early stages of pancreatitis. Presumably, intraacinar cell zymogen activation leads to acinar cell injury and that injury then leads to pancreatitis.

## CLINICAL PRESENTATION

### Symptoms

The classical symptoms of acute pancreatitis are abdominal pain, nausea, and vomiting. The pain is usually experienced in the upper abdomen and usually radiates straight through to the back. It is usually constant and gradually increases in severity. It may be relieved by sitting upright and/or leaning forward. Nausea and vomiting usually follow the onset of pain but the pain is not relieved even by repeated episodes of vomiting. Fever is common but rigors, when they occur, should suggest that biliary obstruction and cholangitis are also present. Clinical jaundice can be present either as a result of biliary tract obstruction or as a result of cholestasis caused by pancreatitis.

### Physical Examination

Acute pancreatitis is usually associated with diffuse abdominal tenderness, and both voluntary and involuntary guarding are typically noted on physical examination. An abdominal mass, particularly in the upper abdomen, can sometimes be felt. The patient is frequently described as "writhing about" on the stretcher in search of a position of comfort. Physical changes indicative of severe dehydration may be present either as the result of repeated vomiting or because of loss of fluid into the extravascular spaces. Tachycardia, fever, tachypnea, and hypotension are commonly seen when pancreatitis is severe. When retroperitoneal hemorrhage has occurred, ecchymoses in the flank (Grey–Turner sign) or periumbilically (Cullen's sign) may be observed. Jaundice is not uncommon, but during the early stages of pancreatitis, the jaundice is usually mild.

### Blood Tests

Routine blood tests usually reveal an elevated white blood cell count and a so-called shift to the left manifested by an increase primarily in neutrophils. The hematocrit is usually elevated as a result of fluid loss, either externally as the result of vomiting or internally as a result of fluid shifts to the extravascular compartment. Measurement of serum electrolytes in the former case usually reveals changes indicative of a hypochloremic alkalosis whereas serum electrolytes may be normal in spite of severe dehydration if most of the fluid has been lost into the extravascular space. In either case, hypoalbuminemia is common. The bilirubin and transaminases may be elevated, and the alkaline phosphatase may be elevated with these changes due either to extrahepatic biliary obstruction or to the cholestasis of severe illness. Patients with hyperlipidemia-induced pancreatitis typically have very high serum triglycerides during an attack and, not infrequently, lactescent serum can be seen. The classical change in blood chemistry associated with acute pancreatitis is a rise in the serum amylase, lipase, or both. The magnitude of these rises does not indicate the severity of the attack and a substantial fraction of patients may be examined in the hospital setting after these changes have resolved and their amylase or lipase levels have returned to normal. It is important to recognize that an elevated amylase can be noted in a variety of disease states other than pancreatitis (see Table II) and that a rise in serum amylase is therefore not necessarily diagnostic of pancreatitis. Similarly, a normal or near-normal serum amylase value does not exclude the diagnosis of acute pancreatitis.

A number of other tests have been proposed for the diagnosis of acute pancreatitis. These include measurement of trypsinogen activation peptide (TAP) in blood or serum, measurement of serum immunoreactive trypsin, measurement of urine amylase levels, and measurement of the clearance ratio of amylase to creatinine. Unfortunately, none of these tests is without false positives or false negatives and, at present, they would appear to have little to offer for the diagnosis of acute pancreatitis. Recent studies have suggested that a

TABLE II Causes of Elevated Serum Amylase Activity

| Pancreatic causes | Intraabdominal nonpancreatic causes | Extraabdominal causes |
|---|---|---|
| Acute pancreatitis | Perforated hollow viscus | Salivary gland pathology |
| Pancreatic ascites | Cholangitis | Burns |
| Pancreatic trauma | Renal failure | Lung tumors |
| Chronic pancreatitis | Mesenteric ischemia/infarction | Diabetic ketoacidosis |
| Pancreatic cancer | Cholecystitis | Pneumonia |
| Endoscopic retrograde cholangiopancreatography | Ruptured ectopic pregnancy | |
| Pseudocysts | Bowel obstruction | |
| Duct obstruction | Ovarian cyst | |

number of blood tests can be used to predict the severity of pancreatitis. These include measurement of serum interleukins (IL-1 and IL-6), tumor necrosis factor α (TNFα), and C-reactive protein. Changes in the levels of these elements are not specific to pancreatitis and these tests should therefore not be used for the diagnosis of pancreatitis.

### Imaging Studies

Plain films of the abdomen usually reveal an ileus pattern. Occasionally, a prominent loop of air-filled jejunum (sentinel loop) near the pancreas is seen in the left upper quadrant of the abdomen, but this is not uniformly the case. On chest X-ray, pleural effusions and lower lobe atelectasis are common. Occasionally, ultrasound examination of the abdomen may be helpful in the diagnosis by revealing pancreatic swelling and the presence of gallbladder and/or bile duct stones. However, ultrasound examination is often incomplete because the dilated, gas-filled bowel loops that are present as the result of pancreatitis-induced ileus may preclude a comprehensive ultrasound exam.

Perhaps the most useful imaging study for acute pancreatitis is the computed tomography (CT) scan, particularly when it is combined with intravenous bolus administration of contrast material. This exam usually detects all but the mildest changes of pancreatitis, including pancreatic swelling, peripancreatic inflammation, the presence of acute peripancreatic fluid collections, and the development of pancreatic necrosis. The latter change is manifested by areas of non-contrast-perfused pancreatic tissue. The contrast-enhanced CT scan can be particularly useful by excluding other causes of severe abdominal pain and peritonitis, including perforated viscus and ischemic bowel. The finding of a normal pancreas on contrast-enhanced CT examination in the presence of clinical changes suggestive of severe pancreatitis should alert the clinician to the high likelihood that the patient does not, indeed, have pancreatitis.

### Prognosis

Several scoring systems have been used in an attempt to determine, early in the course of pancreatitis, whether the attack is mild or severe. These include the Ranson system (see Table III), the Glasgow system, the CT scoring system, and the Acute Physiology and Chronic Health Evaluation (APACHE) scoring system. Obesity has also been identified as an independent risk factor. It is also likely that an experienced clinician using simple "good judgment" can also discriminate between mild and severe pancreatitis with similar accuracy. Patients with severe pancreatitis, for the most part, experience a complex disease with secondary failure of other organs (lungs, kidney, etc.), which often requires prolonged intensive care, may necessitate repeated operations and may be associated with mortality rates of 20–40%. On the other hand, mild pancreatitis is truly a mild disease with recovery in several days, little morbidity, and negligible mortality.

## TREATMENT

### Initial Treatment

The initial treatment of acute pancreatitis includes the firm establishment of a diagnosis. A number of other serious problems, including perforated viscus, ischemic or infarcted bowel, and bowel obstruction, can masquerade as pancreatitis, and making the firm diagnosis of acute pancreatitis may not be a trivial matter. Usually, patients present with classical symptoms, physical findings, and laboratory changes, including hyperamylasemia. An early CT scan can be used to confirm the diagnosis. However, when doubt persists, a diagnostic laparotomy, to exclude other causes of abdominal pain, may be required.

Once the diagnosis of acute pancreatitis is established, attention should be directed at relieving pain and providing fluid resuscitation. The pain of pancreatitis may be severe and difficult to control. It is generally

TABLE III Ranson's Signs for the Prognosis of Acute Pancreatitis[a]

| On admission | During initial 48 hours |
|---|---|
| Age Over 70 Years | Hematocrit decrease over 10% with rehydration |
| White blood cell count over 18,000/mm$^3$ | Blood urea nitrogen rise greater than 2 mg/dl |
| Blood glucose over 20 mg/dl | Serum calcium below 8 mg/dl |
| Lactate dehydrogenase over 400 IU/liter | Arterial oxygen below 60 mmHg |
| Glutamic aspartate aminotransferase above 250 U/liter | Base deficit over 5 mEq/liter |
| | Fluid sequestration over 4 liters |

[a]Adapted from Ranson (1979). The total number of positive items correlates with morbidity and mortality.

believed that meperidine, rather than morphine, is the opiate of choice for pain control in pancreatitis. Fluid requirements, particularly in severe pancreatitis, can be enormous, and, in many ways, resemble those of a severe burn. The hematocrit elevation can be used to estimate the intravascular fluid deficit, and that deficit should be replaced with an isotonic solution containing albumin. Usually, the standard serum electrolytes are normal and fluid replacement can be achieved with either lactated Ringer's solution or normal saline. Hypocalcemia can be present and, if ionized serum calcium levels are depressed, calcium administration may be indicated. Hypomagnesemia, particularly in patients with a history of ethanol abuse, may also be present and require treatment.

Adequate fluid resuscitation is perhaps the single most important element in the early treatment of severe pancreatitis, and there is evidence that inadequate fluid repletion can markedly worsen the severity of a pancreatitis attack. Proper administration of fluid in this setting may require placement of a central venous or pulmonary artery pressure monitor. This is especially true in patients with comorbidities such as cardiac disease and in those with adult respiratory distress syndrome (ARDS), because overhydration in these patients may also create serious problems.

Prophylactic antibiotics may be helpful in the early treatment of patients with severe acute pancreatitis. Several reports have indicated that early administration of broad-spectrum antibiotics that penetrate the pancreas may decrease either the mortality or the morbidity of severe pancreatitis by reducing the incidence of later septic complications. This is a controversial issue, however, because the administration of prophylactic antibiotics may favor the emergence of resistant organisms, particularly fungi, in the inflamed pancreas, actually worsening the clinical course.

Patients with severe pancreatitis may suffer from a prolonged illness, and provision of adequate nutrition is therefore essential. The early institution of total parenteral nutrition in these patients has gained wide acceptance, although, at present, there is considerable interest in providing nutrition via an enteral route. Early enteral nutrition, provided via a nasoenteric or nasogastric tube, may also be beneficial in preventing bacterial translocation from the bowel to the pancreatic bed, thus, in this manner, reducing the incidence of pancreatic infection. Randomized studies to evaluate this possibility are currently underway.

A number of other therapies for pancreatitis have been proposed, frequently on the basis of preclinical animal experiments, but none of these interventions has been shown to be of benefit. Included among these unproved therapies are peritoneal lavage, plasma ultrafiltration, nasogastric suction, and administration of variety of agents, including atropine, glucagon, calcitonin, somatostatin, steroids, protease inhibitors, heparin, and platelet-activating factor antagonists. There is currently great interest in the possibility that agents that modify the inflammatory response by interfering with cytokine/chemokine action may be useful in the early treatment of pancreatitis, and it is likely that prospective trials of such agents will be forthcoming. However, at present, no agents directed at altering the inflammatory response have been of proved benefit in the treatment of severe acute pancreatitis.

The role of early (i.e., within 48–72 hours of the onset of an attack) endoscopic biliary stone clearance, achieved by ERCP, with or without endoscopic sphincterotomy, has been the subject of several prospective randomized trials. Each of those studies has shown that early stone clearance is of no benefit in mild pancreatitis. On the other hand, in severe pancreatitis, early stone clearance has been shown to be of benefit in two studies but of no benefit in a third study. Thus, at present, the role of early stone clearance by ERCP and endoscopic sphincterotomy is controversial.

## Late Treatment of Complications

Acute pancreatitis may be complicated by the late development of pancreatic infection or by the evolution of a pancreatic pseudocyst. Pancreatic infection, when it involves infection of either necrotic pancreatic tissue or necrotic peripancreatic tissue, usually requires surgical debridement. For the most part, this is accomplished by repeated operations, during which the infected necrotic tissue is removed and drains are placed. Recently, attempts to accomplish this by percutaneous or even endoscopic methods have also been described, but the role of those methods remains to be established.

Pancreatic pseudocysts are collections of fluid that are contained within the boundaries created by adjacent structures. Most communicate with the pancreatic ductal system and contain fluid with high concentrations of pancreatic digestive enzymes. They may be colonized by bacteria, but clinical infection, with signs of sepsis, is usually absent. When clinical infection is present, a pancreatic abscess (i.e., infected pseudocyst) should be suspected. Pancreatic pseudocysts that are asymptomatic and of stable size do not require treatment. When infected, they should be drained, usually by percutaneous methods externally. It is generally believed that, in the absence of infection, pseudocysts that are symptomatic and/or enlarging after 6 weeks of observation should be

treated, but there is no agreement as to the ideal method of treating such pseudocysts. Successful treatment has been reported using percutaneous drainage (i.e., with CT or ultrasound guidance), endoscopic internal drainage (i.e., with endoscopic ultrasound guidance), or by surgical internal drainage (i.e., by cyst gastrostomy or cyst Roux-en-Y jejunostomy). In practice, the approach is usually determined by the local expertise available at the treating institution.

## See Also the Following Articles

**Amylase • Computed Tomography (CT) • Pancreatic Digestive Enzymes • Pancreatic Function Tests • Pancreatic Pseudocysts • Pancreatic Triglyceride Lipase • Pancreatitis, Experimental Models • Trypsin • Ultrasonography**

## Further Reading

Banks, P. A. (1993). Medical management of acute pancreatitis and complications. *In* "The Pancreas: Biology, Pathobiology and Disease" (V. L. W. Go, E. P. DiMagno, J. D. Gardner, E. Leventhal, H. A. Reber, and G. A. Scheele, eds.), pp. 593–612. Raven Press, New York.

Beger, H. G., Buchler, M., Bittner, R., Block, S., Nevalainen, T., and Roscher, R. (1988). Necrosectomy and postoperative local lavage in necrotizing pancreatitis. *Br. J. Surg.* 75, 207–212.

DiMagno, E. (1993). Treatment of mild pancreatitis. *In* "Acute Pancreatitis: Diagnosis and Therapy" (E. Bradley III, ed.), pp. 261–264. Raven Press, New York.

Kloppel, G. (1999). Progression from acute to chronic pancreatitis. A Pathologist's view. *Surg. Clin. North Am.* 79, 801–814.

Leavitt, M. D., and Eckfeldt, J. H. (1993). Diagnosis of acute pancreatitis. *In* "The Pancreas: Biology, Pathobiology, and Disease" (V. L. W. Go, E. P. DiMagno, J. D. Gardner, E. Leventhal, H. A. Reber, and G. A. Scheele, eds.), pp. 613–636. Raven Press, New York.

Ranson, J. H. C. (1979). The timing of biliary surgery in acute pancreatitis. *Ann. Surg.* 189, 654–663.

Russell, C. (1998). Long-term prognosis after acute pancreatitis. *In* "The Pancreas" (H. G. Beger, A. L. Warshaw, M. Buchler, D. L. Carr-Locke, J. P. Neoptolemos, C. Russell, and M. G. Sarr, eds.), pp. 656–664. Blackwell Science, London.

Sarr, M. G., Nagorney, D. M., Mucha, P. J. R., Farnell, M. B., and Johnson, C. D. (1991). Acute necrotizing pancreatitis: Management by planned, staged pancreatic necrosectomy/debridement and delayed primary wound closure over drains. *Br. J. Surg.* 78, 576–581.

Sigurdsson, G. J. H. (1998). Necrotizing pancreatitis: Intensive-care measures. *In* "The Pancreas" (H. G. Beger, A. L. Warshaw, M. W. Buchler, D. L. Carr-Locke, J. P. Neoptolemos, and C. Russell, eds.), pp. 508–520. Blackwell Science, London.

Steinberg W., and Tenner, S. (1994). Acute pancreatitis. *N. Engl J. Med.* 330, 1198–1210.

Vitas, G. J., and Sarr, M. G. (1992). Selected management of pancreatic pseudocysts: Operative versus expectant management. *Surgery* 111, 123–130.

# Pancreatitis, Chronic

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**cholecystokinin** A gastrointestinal hormone that stimulates pancreatic secretion of digestive enzymes as well as gallbladder contraction.

**endoscopic retrograde cholangiopancreatography** A procedure utilizing an endoscope to inject radiographic contrast into the pancreatic and bile ducts. Treatment of certain problems including ductal strictures and removal of ductal stones is possible with this technique.

**endoscopic ultrasonography** A procedure utilizing an endoscope with an ultrasound probe mounted on the tip, which allows highly detailed examination of the pancreas and surrounding structures.

**neurolysis** Destruction of nerves to produce pain relief

**pseudoaneurysm** Aneurysmal dilation of a peripancreatic artery produced by the local injurious effects of a pseudocyst.

**pseudocyst** A collection of fluid produced by leakage of pancreatic juice and surrounded by a capsule of fibrous and granulation tissue.

**secretin** A gastrointestinal hormone that stimulates pancreatic secretion of fluid and bicarbonate.

**steatorrhea** The presence of significant undigested fat in the stool. A marker of inadequate or incomplete digestion of fat.

**trypsinogen** A pancreatic digestive enzyme that, once activated, has the capacity to activate all the other pancreatic digestive enzymes.

**trypsin inhibitor protein (also known as SPINK-1)** A pancreatic secretory protein that inhibits the action of activate trypsin and functions as a protective mechanism to prevent inadvertent activation of digestive enzymes within the pancreas.

Chronic pancreatitis is characterized by inflammation, fibrosis, and eventually destruction of both exocrine and endocrine tissue. By definition, the damage is permanent and irreversible. This histological definition, although still widely accepted, is difficult to apply in practice, as pancreatic tissue is rarely available for evaluation. Over a number of years, a series of international panels have attempted to draw up definitions for chronic pancreatitis but these have also been based on histology. More recent attempts to define and categorize chronic pancreatitis have focused on the results of diagnostic tests or on etiology, bypassing the difficult issue of defining the disease. For many clinicians, the definition has been based on abnormalities of the pancreas visible on imaging studies such as computed tomography, ultrasound, or endoscopic retrograde cholangiopancreatography. Unfortunately, these abnormalities (such as diffuse pancreatic calcifications or a dilated pancreatic duct) may take years to develop and may not even develop in some patients. Defining the disease based on imaging studies will therefore miss many patients with the disease. More recent attempts to categorize chronic pancreatitis have focused more on etiology, but no single, widely accepted method for defining and categorizing chronic pancreatitis exists.

## DEMOGRAPHIC FINDINGS

Estimates of the incidence and prevalence of chronic pancreatitis vary widely. Autopsy studies suggest a prevalence of 0.04–5%. Autopsy studies may overestimate true prevalence as histologic changes of chronic pancreatitis can be found in certain subgroups (e.g., long-standing alcohol use, very elderly) in whom no symptoms of chronic pancreatitis were present in life. Incidence studies range from less than 1 to more than 10 new cases per 100,000 population. The single prospective study that was performed found a prevalence of 27.4 cases per 100,000 population and an incidence of 8.2 new cases per 100,000 population. In the United States, this accounts for more than 60,000 hospital admissions yearly in which chronic pancreatitis is one of the discharge diagnoses.

Most of these demographic data are based on patients with alcohol-induced chronic pancreatitis, as these are the easiest to diagnose using routinely available imaging studies. Patients with other forms of pancreatitis (e.g., idiopathic chronic pancreatitis) and those with less advanced cases of alcoholic chronic pancreatitis may lack these easily identifiable abnormalities and so may not be included in epidemiological studies. The true incidence and prevalence are therefore probably higher than the available estimates.

Chronic pancreatitis produces significant morbidity, mortality, and health care costs. A recent analysis of both acute and chronic pancreatitis estimated total

 

costs at 2.5 billion dollars yearly. Morbidity and mortality occur as a consequence of the disease itself, the therapy used to treat it (e.g., surgery), or ongoing alcohol abuse (in those with alcohol-induced chronic pancreatitis). Abdominal pain, maldigestion with weight loss, diabetes mellitus, secondary cancers, and continued alcohol abuse are the major negative influences on quality and length of life. Overall, 10-year mortality is approximately 30% and 20-year mortality is approximately 50% or greater. Death is often not due to chronic pancreatitis but rather to other medical conditions (cirrhosis, malignancy, and vascular disease), continued alcohol abuse, or postoperative complications.

## ETIOLOGY AND PATHOPHYSIOLOGY

Despite intense effort, no clear unifying pathophysiologic mechanisms have been identified. Although all etiologies of chronic pancreatitis may produce similar histologic damage, the pathophysiologic mechanism may vary from etiology to etiology. The ultimate effect is damage to the pancreatic acini, ducts, nerves, and islet cells and the development of the cardinal manifestations of abdominal pain, maldigestion, and diabetes mellitus. The etiologies of chronic pancreatitis are listed in Table I and are discussed below.

### Alcohol Consumption

Alcohol consumption is the major cause of chronic pancreatitis. Although there is no "safe" level of intake below which chronic pancreatitis does not occur, prolonged alcohol intake is usually required (e.g., 4 pints of beer or 800 ml of wine per day for 6–12 years). Only a minority of alcoholics (approximately 15%) drinking this much will actually develop chronic pancreatitis, suggesting that an important cofactor (such as diet or genetics) exists. In Westernized societies, 70% of cases of chronic pancreatitis are due to alcohol consumption, with the remaining 30% due to other causes or idiopathic disease. The mechanism by which alcohol produces pancreatic injury and chronic pancreatitis is unknown.

TABLE I Causes of Chronic Pancreatitis

| |
|---|
| Alcohol abuse |
| Tropical pancreatitis |
| Obstruction of pancreatic duct |
| Trauma to pancreatic duct |
| Benign or malignant ductal stricture |
| Consequences of pancreatic duct stent |
| Pancreas divisum |
| Genetic causes |
| Hereditary pancreatitis (trypsinogen gene mutations and others) |
| Cystic fibrosis |
| Autoimmune chronic pancreatitis |
| Recurrent or severe acute pancreatitis |
| Idiopathic pancreatitis |
| Early-onset |
| Late-onset |

By the time the first clinical attack of alcoholic pancreatitis occurs, most patients have already developed histologic changes of chronic pancreatitis. Continued alcohol abuse leads to ongoing pancreatic damage although damage may continue even with complete abstinence, albeit at a slower rate. The prognosis of alcoholic chronic pancreatitis is poor, with the frequent development of exocrine or endocrine insufficiency and increased mortality due to the consequence of continued alcohol abuse.

### Tropical Pancreatitis

Tropical pancreatitis is the most common form of chronic pancreatitis in certain areas of Indonesia, India, and Africa. The most classic form includes abdominal pain beginning in childhood, with subsequent diabetes, malnutrition, and diffuse pancreatic calcifications. Less severe forms also seem to exist. Most people ultimately die from complications of the disease. Malnutrition is felt to be important in the development of tropical chronic pancreatitis, perhaps due to deficiencies in trace elements or antioxidants. Toxic products contained in the diet (e.g., cassava or sorghum) or the environment or genetics may also play a role in pancreatic injury.

### Pancreatic Duct Obstruction

Any condition that chronically obstructs the main pancreatic duct can lead to chronic pancreatitis in the gland "upstream" from the obstruction. Obstruction may be due to benign strictures, ampullary stenosis or neoplasms, pancreatic tumors or pseudocysts, congenital variants, or endoscopically placed pancreatic duct stents. Long-standing obstruction leads to irreversible chronic pancreatitis, but both functional and structural improvement can be seen if the obstruction is discovered and relieved.

One form of pancreatic duct obstruction deserves specific mention. Pancreas divisum, a congenital failure of fusion of the dorsal and ventral pancreatic ducts, may lead to obstruction of the pancreatic duct and chronic pancreatitis. The small ventral pancreas drains through the larger major papilla and the larger dorsal pancreas drains through the smaller accessory papilla. Pancreas

divisum occurs in up to 7% of the population. Although the vast majority of patients with this congenital abnormality have no symptoms, a small subset of patients will develop acute or chronic pancreatitis.

## Genetic Forms of Chronic Pancreatitis

### *Hereditary Pancreatitis*

Several kindreds from around the world with acute and chronic pancreatitis have been described. The pattern of inheritance is autosomal dominant with incomplete penetrance and the typical clinical features are recurrent acute pancreatitis beginning at an early age, culminating in advanced chronic pancreatitis. Pancreatic cancer is a common complication, occurring in up to 40% of these patients. There are a number of genetic defects that have been identified in these kindreds with hereditary pancreatitis. Functional genomic studies initially identified a single point mutation in the cationic trypsinogen gene. Trypsinogen is a proenzyme that, once activated, has the ability to activate not only itself but other digestive enzymes as well. In the normal state, trypsinogen is activated only within the duodenum, safely away from the pancreas. Trypsinogen may, however, undergo a very slow autoactivation within the pancreas. A number of mechanisms exist to prevent this activated trypsin from activating other digestive enzymes within the pancreas and causing pancreatitis. Based on molecular modeling, the mutation was thought to convey a gain-of-function mutation, in which the mutated trypsinogen was resistant to inactivation once activated. Trypsin, the activated form of trypsinogen, could then activate all of the other pancreatic digestive enzymes within the pancreas. This continual low-grade activation of digestive enzymes within the pancreas is believed to produce ongoing damage, which ultimately produces severe chronic pancreatitis. Since this initial discovery, several other gene mutations have been identified in the cationic trypsinogen gene as well as within an enzyme meant to inactivate trypsin, the trypsin inhibitor protein (serine protease inhibitor kazal type 1 or SPINK-1). Studies have not yet identified these gene mutations as being important in patients with other forms of chronic pancreatitis (idiopathic and alcoholic chronic pancreatitis).

### *Cystic Fibrosis*

In children, cystic fibrosis is the most common cause of pancreatic insufficiency. Precipitation of protein plugs and inspissated mucus occur in the pancreatic duct, much as in the bronchioles, leading to damage to the gland due to chronic obstruction. Recent studies have noted cystic fibrosis gene mutations in patients with acute and chronic pancreatitis who have no pulmonary or sinus conditions commonly associated with cystic fibrosis. In some studies, at least half of patients initially diagnosed with "idiopathic" chronic pancreatitis have at least one cystic fibrosis allelic mutation. Many of these mutations are not measured on commercially available screens and complete genetic analysis is required to identify the mutations.

## Rare Forms of Chronic Pancreatitis

### *Autoimmune Chronic Pancreatitis*

Chronic pancreatitis may rarely be seen in association with autoantibodies, elevated levels of immunoglobulins, and dense lymphocytic infiltrate within the pancreas (if histology is available). In over half of these cases, other autoimmune diseases coexist including primary sclerosing cholangitis, primary biliary cirrhosis, autoimmune hepatitis, and Sjogren's syndrome.

### *Recurrent or Severe Acute Pancreatitis*

A very severe attack of acute pancreatitis or multiple less severe attacks may produce enough damage to the gland to result in chronic pancreatitis. Most commonly, this occurs after the development of a stricture in the pancreatic duct that produces continuing damage to the gland upstream of the stricture.

### *Hypertriglyceridemia*

Triglyceride levels above 1000 mg/dl can initiate acute pancreatitis. Recurrent attacks of hyperlipidemic pancreatitis may ultimately produce chronic pancreatitis. This occurs most commonly as a result of familial hyperlipidemias (types IV and V) exacerbated by estrogen use or poorly controlled diabetes. This cause of both acute and chronic pancreatitis should not be forgotten, as effective therapy is available.

## Idiopathic Chronic Pancreatitis

Between 10 and 30% of patients will not have an easily definable cause of chronic pancreatitis. Idiopathic chronic pancreatitis is the second most common cause of chronic pancreatitis in adults, behind alcohol abuse. Some of these patients may actually be alcoholics and may be missed if this history cannot be elucidated. Some may have cystic fibrosis gene mutations, as noted above. Two different forms of idiopathic chronic pancreatitis have been described, a late-onset form and an early-onset form. The late-onset form occurs at a mean age of 56 years, commonly presenting with steatorrhea or diabetes and less commonly with abdominal pain. The early-onset form begins at approximately age 20 and is

characterized by severe pain in essentially all patients but very infrequently by steatorrhea or diabetes. Many of these patients with early-onset idiopathic chronic pancreatitis do not have easily identifiable abnormalities of the pancreas on imaging studies [computed tomography (CT), ultrasound (US), or endoscopic retrograde cholangiopancreatography (ERCP)] and are commonly misdiagnosed.

## CLINICAL FEATURES

### Abdominal Pain

Abdominal pain is the predominant symptom of chronic pancreatitis and the one that most adversely affects quality of life. The most frequent type of pain is dull, located in the epigastrium with associated back pain, and made worse by eating or lying in the supine position. Food may be avoided, leading to weight loss and malnutrition. Pain may be episodic (lasting from hours to weeks) or more constant or continuous. The pain is generally moderate to severe and narcotic analgesics are required in many patients. Pain is not universal, however. Pain never develops in up to 15% of patients with alcoholic chronic pancreatitis and up to 25% (or more) of patients with late-onset idiopathic chronic pancreatitis. In some patients, the pain may "burn out" after many years of chronic pancreatitis, although this is unpredictable.

There are many potential sources of pain. The most common contributing factors are considered to be inflammation and damage to pancreatic and peripancreatic visceral afferent nerves, pancreatic tissue ischemia, hyperstimulation of the pancreas due to interruption of normal feedback control, and complications of chronic pancreatitis (pseudocyst, common bile duct or duodenal obstruction, superimposed pancreatic carcinoma).

### Maldigestion

Exocrine insufficiency (steatorrhea) due to chronic pancreatitis does not occur until the capacity of the pancreas to secrete lipase and colipase is reduced to less than 10% of normal. Maldigestion is thus a marker of far-advanced chronic pancreatitis. Fat maldigestion is more common and more clinically important than protein or carbohydrate maldigestion. Maldigestion is due to diminished secretion of pancreatic enzymes as well as reduced secretion of bicarbonate from the pancreatic ductal system; with reduced bicarbonate, the lower duodenal pH inactivates many pancreatic digestive enzymes. Weight loss is not invariable with maldigestion as intake may be increased, but can occur if food is avoided due to pain or if intake is inadequate due to chronic alcoholism. Folate deficiency may be seen, particularly in chronic alcoholics. Osteopenia and osteoporosis may also develop as a consequence of vitamin D deficiency.

### Diabetes Mellitus

Endocrine insufficiency (diabetes mellitus) develops when enough pancreatic islet cells have been destroyed to significantly impair insulin production. The islet cells are more resistant to damage than the acinar and ductal cells, so diabetes is also a marker of far-advanced chronic pancreatitis. This form of diabetes is rarely associated with ketoacidosis but frequent treatment-associated episodes of hypoglycemia can occur (due to inadequate glucagon reserves). Microvascular complications of diabetes (retinopathy or neuropathy) occur as frequently as in other diabetics, if corrected for the duration of disease.

## DIAGNOSIS

Clinical features such as abdominal pain, steatorrhea, or diabetes usually suggest the possibility of chronic pancreatitis, and this is confirmed by one of a wide variety of diagnostic tests. The true gold standard diagnostic test, pancreatic histology, is rarely available and alternative tests serve as imperfect substitutes. Most of the diagnostic tests currently in use are imaging studies that detect structural abnormalities within the pancreas. These can include such features as a dilated or irregular pancreatic duct, pancreatic gland atrophy, or diffuse pancreatic calcifications. Chronic pancreatitis can be a slowly progressive disease and these changes may take years to develop. Similarly, functional problems such as exocrine or endocrine insufficiency may not develop for years. In advanced and long-standing disease, easily visible structural and functional abnormalities may be seen and this makes the diagnosis straightforward. In less advanced disease or disease of shorter duration, however, these structural and functional changes may not be present and the diagnosis can be challenging. This has led to a general clinical differentiation: "big-duct disease" and "small-duct disease." Big-duct disease is the presence of significant structural abnormalities of the pancreas (dilation of the main pancreatic duct, diffuse calcifications) and is often associated with exocrine or endocrine insufficiency. Small-duct disease implies the absence of these advanced structural abnormalities and usually the absence of exocrine or endocrine insufficiency. This differentiation is clinically useful; those with big-duct disease have advanced or long-standing disease, are easiest to diagnose, are usually alcoholic,

TABLE II Diagnostic Tests and Studies for Chronic Pancreatitis (Listed in Order of Decreasing Sensitivity)

| Tests of function | Procedures examining structure |
|---|---|
| Secretin or secretin–cholecystokinin test | EUS[a] |
| Fecal elastase or chymotrypsin | ERCP |
| Serum trypsin | MRI/MRCP[a] |
| Fecal fat | CT |
| Blood glucose | Ultrasound |
| | Plain abdominal radiograph |

[a] Estimated. The sensitivity of EUS may be better than that of ERCP, MRI, and CT. The specificity of EUS is, however, suboptimal and limits its overall accuracy. The sensitivity of MRI/MRCP is not known but is still probably less than that of ERCP using current image technology.

and are most suitable for endoscopic or surgical therapy. Those with small-duct disease are much more difficult to diagnose, are more likely idiopathic, and are most suitable for medical therapy.

Very few diagnostic tests measure abnormalities of pancreatic function. With the exception of direct hormonal stimulation testing, these tests of function are abnormal only in far-advanced disease when exocrine insufficiency has already developed. Diagnostic tests used for chronic pancreatitis are listed in Table II and are discussed below.

## Tests of Pancreatic Structure

### *Plain Abdominal X Rays*

The finding of diffuse pancreatic calcification on a plain abdominal radiograph is specific for chronic pancreatitis but is seen only in far-advanced disease. Focal pancreatic calcification may be due to other conditions such as trauma, islet-cell tumors, or hypercalcemia.

### *Abdominal Ultrasonography and Computed Tomography*

A transabdominal ultrasound may note pancreatic parenchymal calcifications, pancreatic atrophy, or a dilated pancreatic duct. Overlying bowel gas can interfere with visualization of the pancreas, making the sensitivity of ultrasound greater than that of plain X rays but less than that of CT. CT findings of chronic pancreatitis include atrophy of the gland, irregular contour of the pancreas, dilation or irregularity of the pancreatic duct, and calcified pancreatic calculi (Fig. 1). CT is also useful in looking for complications of chronic pancreatitis (e.g., pancreatic carcinoma or pancreatic pseudocyst).

### *Magnetic Resonance Imaging and Magnetic Resonance Cholangiopancreatography*

The quality of standard magnetic resonance imaging (MRI) images of the pancreas continues to improve but has not yet reached the overall quality of CT. Magnetic resonance cholangiopancreatography (MRCP) utilizes an anatomic reconstruction of the biliary and pancreatic ductal systems. MRCP is most accurate in advanced chronic pancreatitis but the accuracy with less-advanced chronic pancreatitis is substantially reduced.

### *Endoscopic Ultrasonography*

The endoscopic ultrasonography (EUS) instrument is a high-frequency ultrasound probe mounted on an endoscope. High-resolution images can be acquired of the pancreatic duct, parenchyma, and surrounding structures. EUS is highly accurate in advanced chronic pancreatitis (Fig. 2). The sensitivity and especially the specificity of the test in patients without these advanced abnormalities are not yet known.

### *Endoscopic Retrograde Cholangiopancreatography*

ERCP is one of the most commonly used imaging techniques in the evaluation of patients with presumed chronic pancreatitis. The procedure involves injection of the pancreatic duct with radiographic contrast. The diagnosis of chronic pancreatitis by ERCP is based on changes in the main pancreatic duct and the duct side branches. These changes include duct dilation, stricture formation, irregular duct contour, associated filling of

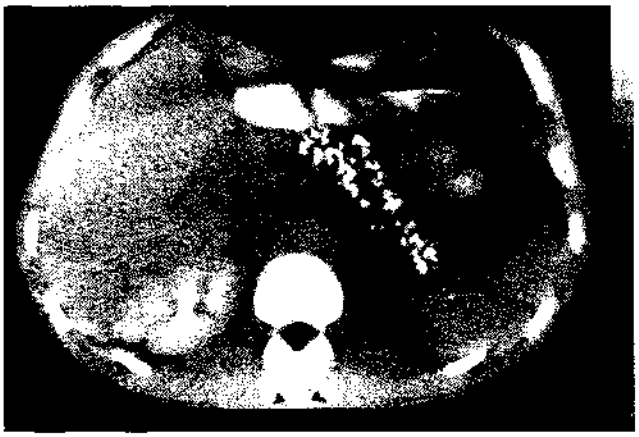

FIGURE 1 An abdominal CT scan demonstrates diffuse and dense calcification within the pancreas of a patient with long-standing alcohol-induced chronic pancreatitis.

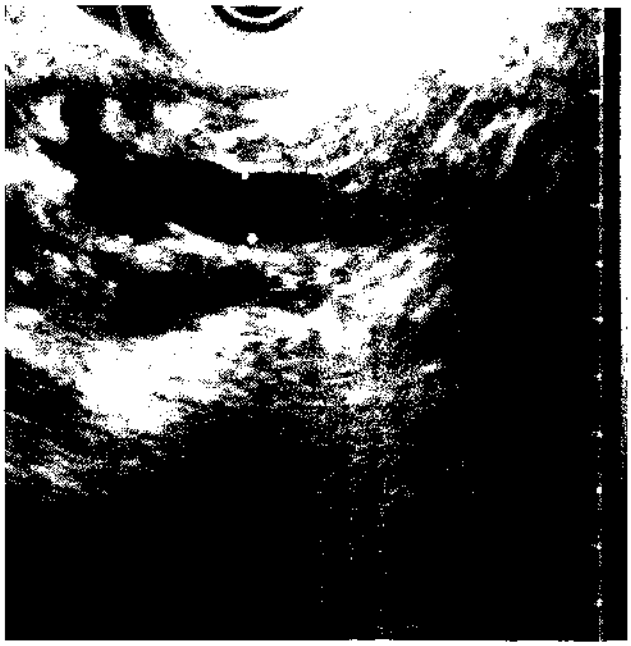

FIGURE 2 An EUS image of chronic pancreatitis. The instrument is seen at the top of the image. The dilated pancreatic duct (measurement markers) is seen at the bottom. The parenchyma of the gland between the scope and dilated duct has irregular echotexture, also consistent with chronic pancreatitis.

cavities or pseudocysts, and filling defects (i.e., pancreatic ductal calculi). ERCP is highly accurate in advanced disease and reasonably accurate in less severe disease (Fig. 3). Some patients, however, can have chronic pancreatitis with a normal ERCP. ERCP is also limited by a number of clinical considerations. In up to one-third of procedures, the ERCP image obtained is of inadequate quality to allow a definitive conclusion. Other conditions can mimic the ERCP changes seen in chronic pancreatitis (pancreatic carcinoma, acute pancreatitis, pancreatic duct stenting, and aging). The procedure is expensive and requires substantial experience and skill and procedure-related complications can occur in up to 10% of patients. Given these factors, ERCP is usually a late step in the evaluation of patients with suspected chronic pancreatitis. ERCP does have one advantage in that therapy can also be accomplished in some patients. This therapeutic, rather than diagnostic, role of ERCP is discussed below.

## Test of Pancreatic Function

### *Laboratory Tests*

Serum amylase or lipase levels are often normal and also not of diagnostic importance. Serum trypsin (another pancreatic enzyme) is more useful as a diagnostic test. Levels below 20 mg/dl are seen in advanced chronic pancreatitis (i.e., steatorrhea is present). Pancreatic enzymes may also be measured in stool. Since these enzymes are not reabsorbed, diminished levels in stool are an indirect measure of output of pancreatic enzymes. Both fecal elastase and fecal chymotrypsin have been measured, but only fecal elastase is commercially available. Overall, the sensitivity approaches 90% in advanced disease but is only approximately 50–60% in less advanced disease. This is equivalent to the accuracy of serum trypsin. Measurement of serum glucose or 72 h fecal fat output can document endocrine or exocrine insufficiency but are not useful for diagnostic purposes.

### *Indirect Tests of Pancreatic Function*

There are a number of methods to indirectly measure pancreatic function. Usually, a substrate that requires the presence of pancreatic digestive enzymes within the gut lumen for metabolism is given. Metabolic products are then measured; their relative production rate indirectly reflects pancreatic enzyme secretion. Maldigestion of these substrates does not occur until overall exocrine insufficiency has developed; hence, these tests will be accurate in advanced or end-stage disease but inaccurate in earlier disease. Many variations of this type of test have been developed using a

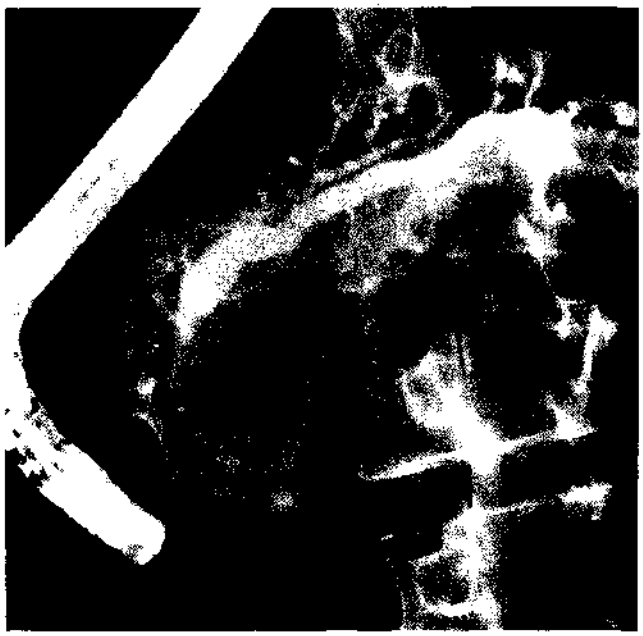

FIGURE 3 An ERCP of a patient with chronic pancreatitis. The scope can be seen, along with a pancreatic duct filled with radiographic contrast. The pancreatic duct is dilated and the side branches of the duct are also dilated and irregular. The findings are consistent with chronic pancreatitis and demonstrate big-duct disease (see text for explanation).

variety of substrates (bentiromide test, pancrealaury test, Lundh test meal, amino acid consumption test, and dual-label Schilling test). None of these tests is available for routine clinical use.

#### *Direct Tests of Pancreatic Function*

These tests measure the actual output from the pancreas after stimulation with a secretagogue. The secretagogues used are secretin, cholecystokinin, or both. Pancreatic secretions are collected with a tube placed in the duodenum. The sensitivity of these tests, like all diagnostic tests, depends on the severity of the disease. The overall sensitivity (74–90%) and specificity (80–90%) are however, superior to those of any other currently available diagnostic test. There are substantial data indicating that direct hormonal stimulation tests can also diagnose chronic pancreatitis at a somewhat earlier stage than any other available test. Unfortunately, these tests are available at only a few referral centers and are unavailable to many clinicians.

### Diagnostic Strategy

The ideal test would have high sensitivity (in both small-duct and big-duct disease) and specificity and be inexpensive, safe, and widely available. No ideal diagnostic test exists. The appropriate use of the variety of available tests requires an understanding of their sensitivity, cost, and risk. Initially, tests that are safe, simple, and inexpensive are used. These tests generally are able to identify only patients with advanced or big-duct chronic pancreatitis. Such tests could include serum trypsin, fecal elastase, and US. When these first-echelon tests are not diagnostic, more invasive, risky, or costly tests would be considered. Second-echelon tests include hormonal stimulation tests, CT scan, MRI/MRCP, or EUS. The most invasive and risky test, ERCP, is most commonly used when the diagnosis remains unclear or when therapy, rather than diagnosis, is required.

## TREATMENT

### Treatment of Exocrine and Endocrine Insufficiency

#### *Steatorrhea*

Steatorrhea occurs only when 90% of pancreatic output has been lost, due to inadequate delivery of both lipase and bicarbonate. The acidic environment further inactivates what lipase may be present and precipitates bile salts, worsening fat absorption. The replacement of endogenous digestive enzymes with exogenous enzymes is the goal of therapy. The use of appropriate dosages of these enzymes leads to resolution of diarrhea and weight loss, although steatorrhea is rarely completely corrected.

The various commercially available preparations and their lipase content are listed in Table III. At least 30,000 IU of lipase needs to be delivered to the duodenum during each meal. Patients using the lower-potency preparations must therefore take three to four pills with each meal. Fewer pills must be taken with the more potent formulations. The enteric-coated preparations are protected from gastric acid. The non-enteric-coated preparations will be destroyed by gastric acid and so must be used in conjunction with an agent to reduce gastric acid output (histamine-2 receptor antagonists or proton pump inhibitors). The most common reason for failure of these enzymes to correct steatorrhea is inadequate dose, usually due to the patient's unwillingness to take the number of pills required. Another common reason is inactivation of lipase by gastric acid in those receiving non-enteric-coated preparations. Dietary manipulations may be needed in the management of malabsorption and malnutrition. The diet should usually contain a moderate percentage of fat (30%), a high percentage of protein (30%), and a low percentage of carbohydrates (40%) and should be supplemented with a high-quality multivitamin, calcium, and vitamin D.

**TABLE III Commercially Available Pancreatic Enzymes for the Treatment of Steatorrhea[a] or Pain[b]**

| Brand name | Units of lipase per pill |
|---|---|
| **Non-enteric-coated enzyme preparations** | |
| Viokase, Viokase 16 | 8,000; 16,000 |
| Ku-Zyme HP | 8,000 |
| Generic pancrealipase | 8,000 |
| **Enteric-coated enzyme preparations** | |
| Creon 5, 10, 20 | 5,000; 10,000; 20,000 |
| Pancrease MT 4, 10, 16, 20 | 4,000; 10,000; 16,000; 20,000 |
| Ultrase 6, 12, 18, 20 | 6,000; 12,000; 18,000; 20,000 |

[a] For the treatment of steatorrhea, both non-enteric-coated and enteric-coated preparations can be used. The dosage depends on the lipase content; 30,000 units of lipase should be delivered with each meal. Non-enteric-coated enzymes require cotreatment with agents to suppress gastric acid.

[b] For the treatment of pain, only non-enteric-coated enzyme preparations are used: four to eight pills (depending on potency) before meals and at night. As above, an adjuvant agent to reduce gastric acid is required.

### *Diabetes Mellitus*

Diabetes is late complication of chronic pancreatitis. Microangiopathic complications occur with regularity, including retinopathy, nephropathy, neuropathy, and more rapid atherosclerosis. Another common complication is treatment-induced hypoglycemia. These patients can have inadequate glucagon as well as insulin reserves and cannot respond to hypoglycemia with a glucagon surge and subsequent increase in blood glucose levels. Overly vigorous attempts to control blood sugar can be associated with disastrous complications of treatment-induced hypoglycemia.

Some patients will respond to oral hypoglycemics, but many require insulin. The goal of insulin therapy is usually to control urinary losses of glucose rather than attempt tight control of blood sugar. Tight control of blood sugar is usually indicated in only one subgroup, those with hyperlipidemic pancreatitis, where tight control of blood sugar is needed to allow control of triglyceride levels.

## Pain

### *Medical Treatment*

There are many causes of pain and no single treatment is effective in all patients. Abstinence from alcohol reduces the risk of other alcohol-related complications such as cirrhosis, prolongs life, slows the rate of progression of chronic pancreatitis, and may reduce pain. Analgesics are routinely required. Nonnarcotic analgesics should be used first and if narcotics are required, the least potent formulation should be tried first (e.g., propopxyphene with acetaminophen, tramadol). More potent narcotics are required in many patients and addiction occurs in up to 20% of these patients. In patients who require narcotics, the addition of an antidepressant (tricyclic antidepressants or selective serotonin reuptake inhibitors) can be helpful as these can potentiate the effect of narcotics.

Several small studies have suggested that nonenteric-coated pancreatic enzymes can reduce abdominal pain in some patients with chronic pancreatitis. The theoretical basis of their effect is to reduce pancreatic stimulation (or hyperstimulation) by cholecystokinin. This effect, of reestablishing normal negative feedback control of pancreatic secretion, is operative only in the duodenum. Enteric-coated preparations typically release their enzymes in the jejunum; hence, non-enteric-coated preparations are selected if the intent is to treat pain. The response in these trials is mixed. Patients who seemed to respond best to the use of conventional enzymes are those with mild to moderate chronic pancreatitis (without steatorrhea or small-duct disease). Patients with advanced disease (steatorrhea or big-duct disease) did not seem to respond. If tried, this therapy should be considered only in select patients (small-duct disease, no steatorrhea) and should use the correct enzyme and the correct dose (non-enteric-coated preparations at high dosage, coupled with an agent to reduce gastric acid).

A few small studies of octreotide (Sandostatin) have suggested that the use of this agent may reduce the pain of chronic pancreatitis, perhaps by reducing pancreatic stimulation or perhaps by a direct anti-nociceptive effect. A few small studies have also suggested that the use of antioxidants (mixtures of vitamins E and C, selenium, methionine, and β-carotene) may reduce pain. Neither treatment is currently recommended outside clinical trials.

### *Neurolysis*

Interruption of nociceptive visceral afferents from the pancreas can be accomplished by ablation of the celiac nerve plexus. This has been tried by both CT-guided and EUS-guided methods, using injection of anesthetics, steroids, or alcohol. The therapy seems most effective for the pain of pancreatic cancer but is usualy too short-lived for patients with chronic pancreatitis. EUS-guided techniques appear to work better and for somewhat longer periods of time than CT-guided techniques. Destruction of visceral afferents by destruction of the splanchnic nerves (thoracoscopic splanchnicectomy) is also being investigated but the efficacy remains to be established.

### *Endoscopic Therapy*

Available endoscopic therapies include pancreatic duct sphincterotomy, pancreatic duct stenting, dilation of ductal strictures, removal of pancreatic stones, and treatment of complications such as pseudocyst or biliary obstruction. The primary goal of endoscopic therapy is to remove or bypass any obstruction within the pancreatic duct. Careful selection of patients for this therapy is critical. Appropriate candidates are those with a significant pancreatic ductal stricture in the head of the pancreas or those with a few obstructing stones in the head of the gland. Approximately one-third to one-half of patients with big-duct disease satisfy these criteria. In these carefully selected groups, up to three-fourths of patients will experience pain relief after endoscopic therapy. Complications of endoscopic treatment of chronic pancreatitis occur in 15–20% of patients (pancreatitis, bleeding, perforation, and sepsis). Pancreatic stents, used for therapy in these patients, can in and of themselves also injure the pancreatic duct and

parenchyma in up to half of patients treated, and these changes may not resolve. Endoscopic therapy is a reasonable alternative in appropriately selected patients at centers with appropriate expertise.

### *Surgical Treatment*

Surgical therapy is considered for pain and for complications of chronic pancreatitis (pseudocyst, bile duct obstruction, and duodenal obstruction). The most commonly performed operation for pain is the lateral pancreaticojejunostomy (modified Puestow procedure). The dilated pancreatic duct is longitudinally incised along its length and overlaid with a defunctionalized Roux limb. The procedure carries low rates of complications (5%) and mortality (2%). The pancreatic duct must usually be dilated to greater than 5 mm; hence, this type of surgery is considered in those with big-duct disease. After a Puestow procedure, immediate pain relief occurs in 70–90% of patients. Pain is controlled in only 50% after 1–3 years of follow-up. In some centers, resection of all or part of the head of the pancreas is combined with a ductal drainage procedure. Morbidity and mortality from these operations is higher than that seen with a Puestow procedure, but long-term pain relief is also higher. Subtotal or total pancreatic resections are rarely indicated and are currently associated with unacceptable postoperative complications, particularly brittle diabetes mellitus.

### *Treatment for Pain*

No single therapy is effective in all patients and the choice of a treatment depends on a variety of factors. The most important include pancreatic ductal anatomy, presence of complications, and local expertise. The first step is to make sure the diagnosis is correct. It is inappropriate to consider therapies with potential side effects or complications unless the diagnosis is secure. Second, it is worthwhile to look for specific complications that have specific therapy, such as pancreatic pseudocyst, duodenal obstruction, common bile duct obstruction, peptic ulcer disease, or pancreatic carcinoma (these are discussed below). Medical therapy is appropriate in all patients. This should include encouragement of abstinence from alcohol (if applicable), a low-fat diet, and analgesics. The choice of subsequent therapy depends in large part whether the patient has small-duct or big-duct disease. In those with small-duct disease, a trial of high-dose non-enteric-coated enzymes coupled with acid suppression is appropriate. Treatment options for those with big-duct disease are largely mechanical, with either endoscopic or surgical attempts to decompress the enlarged pancreatic duct. Patients who fail the above therapies may be considered for more experimental therapies such as celiac plexus block, splanchnicectomy, or octreotide. Significant pancreatic resections are considered an option of last resort in both groups of patients.

## COMPLICATIONS

### Pancreatic Pseudocyst

Approximately one-quarter of patients with chronic pancreatitis develop a pseudocyst. Many pseudocysts remain asymptomatic. Symptomatic pseudocysts may obstruct a surrounding hollow viscus (duodenum producing nausea and vomiting or common bile duct producing jaundice), may cause pain, may bleed (internally or into the gut lumen), or may rupture (into the peritoneal cavity producing pancreatic ascites or into the pleural space producing a pancreatic pleural effusion). Overall, these complications occur in approximately one-third of patients. The diagnosis is best made with CT. The diagnosis is usually suspected due to a worsening pattern of pain, persistent elevations in amylase or lipase, or symptoms pointing toward one of the above complications.

Not all pseudocysts require treatment. Those that are less than 6 cm in diameter, that are causing no symptoms, and that occur in a reliable patient can be safely observed. Symptomatic pseudocysts can be managed with percutaneous, endoscopic, or surgical decompression, depending on location and local expertise.

Two complications deserve specific mention. Bleeding is rare but can be life-threatening. Bleeding can occur from a pseudoaneurysm associated with a pseudocyst. Evidence of gastrointestinal bleeding in a patient with a pseudocyst is usually treated as an emergency. If initial evaluations do not reveal a source, an emergent CT is performed to look for a pseudoaneurysm. Confirmation of the pseudoaneurysm with CT should be followed with emergent angiography and embolization. Rupture of a pseudocyst or leak from the pancreatic duct can produce pancreatic ascites of a pancreatic pleural effusion. These should be suspected when a very high level of amylase (typically >4000 IU/liter) is found in ascites or a pleural effusion. Endoscopic treatment at ERCP, with sphincterotomy and stenting, is usually curative. Surgical therapy is reserved for failure of endoscopic therapy.

Pseudocysts should not be mistaken for cystic neoplasms. These neoplasms usually have a thick wall or internal nodules along the wall, often with internal sepatations. They most frequently occur in middle-aged women without previous pancreatitis and without risk factors for pancreatitis. These neoplasms are

frequently misdiagnosed; the therapy is resection, not drainage.

### Gastrointestinal Bleeding

Bleeding may occur not only as a consequence of a pseudoaneurysm (as noted above) but also from thrombosis of the splenic vein as it travels behind the pancreas. This produces a "left-sided" portal hypertension with gastric varices out of proportion to esophageal varices. Splenectomy is curative.

### Pancreatic Carcinoma

Chronic pancreatitis is a risk factor for pancreatic adenocarcinoma and the two may coexist. The overall risk is approximately 4% lifetime, although this may increase to 40% for those with hereditary pancreatitis. There is no currently effective screening method, but superimposed carcinoma is usually suspected due to weight loss or a worsening in a previously stable pain pattern.

### Duodenal or Common Bile Duct Obstruction

Obstruction of the duodenum or intrapancreatic common bile duct may occur due to fibrosis and inflammation within the head of the pancreas or due to an associated pseudocyst. Duodenal obstruction produces nausea, vomiting, and early satiety and is best confirmed by a barium upper gastrointestinal series. Common bile duct obstruction can produce jaundice, biliary pain, cholangitis, or asymptomatic elevations in liver chemistries. These patients may also have intrinsic liver disease, so a liver biopsy is usually indicated before deciding on treatment for asymptomatic elevations in liver chemistries. All other symptomatic presentations require therapy. Endoscopic biliary stenting is an appropriate temporizing measure but these patients generally require surgical biliary bypass.

### Others

Small bowel bacterial overgrowth and gastroparesis may complicate chronic pancreatitis. Both can interfere with effective treatment of steatorrhea and gastroparesis may cause pain of its own accord.

## See Also the Following Articles

**Amylase • Computed Tomography (CT) • Cystic Fibrosis • Diabetes Mellitus • Magnetic Resonance Imaging (MRI) • Malabsorption • Pancreatic Bicarbonate Secretion • Pancreatic Digestive Enzymes • Pancreatic Function Tests • Pancreatic Pseudocysts • Pancreatic Triglyceride Lipase • Trypsin • Ultrasonography**

## Further Reading


Ammann, R. W., Heitz, P. U., and Kloppel, G. (1996). Course of alcoholic chronic pancreatitis: A prospective clinicomorphological long-term study. *Gastroenterology* **111**, 224–231.

Ammann, R. W., and Muellhaupt, B. (1999). The natural history of pain in alcoholic chronic pancreatitis. *Gastroenterology* **116**, 1132–1140.

Cohn, J. A., Bornstein, J. D., and Jowell, P. S. (2000). Cystic fibrosis mutations and genetic predispositions to idiopathic chronic pancreatitis. *Med. Clin. North Am.* **84**, 621–631.

Eisen, G. M., Chutkan, R., Goldstein, J. L., *et al.* (2000). Endoscopic therapy of chronic pancreatitis. ASGE position paper. *Gastrointest. Endosc.* **52**, 843–848.

Etemad, B., and Whitcomb, D. C. (2001). Chronic pancreatitis: Diagnosis, classification, and new genetic developments. *Gastroenterology* **120**, 682–707.

Forsmark, C. E. (2000). The diagnosis of chronic pancreatitis. *Gastrointest. Endosc.* **52**, 293–298.

Forsmark, C. E., and Grendell, J. H. (1991). Complications of pancreatitis. *Semin. Gastrointest. Dis.* **2**, 165–176.

Forsmark, C. E., and Toskes, P. P. (1995). What does an abnormal pancreatogram mean? *Gastrointest. Endosc. Clin. North Am.* **5**, 105–124.

Layer, P., Yamamoto, H., Kalthoff, L., *et al.* (1994). The different courses of early- and late-onset idiopathic and alcoholic chronic pancreatitis. *Gastroenterology* **107**, 1481–1487.

Lowenfels, A. B., Maisonneuve, P., Cavallini, G., *et al.* (1993). Pancreatitis and the risk of pancreatic cancer. *N. Engl. J. Med.* **328**, 1433–1437.

Saforkas, G. H., Farnell, M. B. Farley, D. R., *et al.* (2000). Long-term results after surgery for chronic pancreatitis. *Int. J. Pancreatol.* **27**, 131–142.

Vitas, G. J., and Sarr, M. G. (1992). Selected management of pancreatic pseudocysts: Operative versus expectant management. *Surgery* **111**, 123–130.

Wallace, M. B., and Hawes, R. H. (2001). Endoscopic ultrasound in the evaluation and management of chronic pancreatitis. *Pancreas* **23**, 26–35.

Warshaw, A. L., Banks, P. A., and Fernandez-del Castillo, C. (1998). AGA technical review: Treatment of pain in chronic pancreatitis. *Gastroenterology* **115**, 763–776.

# Pancreatitis, Experimental Models

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acute pancreatitis Acute inflammatory disease of the pancreas.

caerulein An analogue of cholecystokinin that, because it is more stable, is used for secretagogue-induced pancreatitis.

CDE diet Choline-deficient diet supplemented with ethionine; this diet induces pancreatitis in female mice.

sodium taurocholate A bile salt that induces pancreatitis when injected retrograde into the pancreatic duct.

trypsin The pancreatic digestive enzyme whose premature activation within the pancreas is a common feature of various models of pancreatitis.

**Acute pancreatitis is an inflammatory disease of the pancreas that is associated with little or no fibrosis. It can be initiated by several factors including gallstones, alcohol, trauma, and infections and in some cases it may be hereditary. Very often, the patients develop additional complications, such as sepsis, shock, and respiratory and renal failure, resulting in considerable morbidity and mortality. Approximately 300,000 cases occur in the United States each year; some 20% of cases are severe. Despite considerable work being carried out in this area, the pathophysiological mechanisms associated with this disease still remain incompletely understood. This can be attributed in part to the relative inaccessibility of clinical material for experimental studies and has therefore led to the development of several models of experimental pancreatitis to explore its etiology, pathophysiology, and treatment regimens. This article will focus on the experimental models used to study acute pancreatitis. For the sake of simplicity, these models have been divided into two broad categories depending on the approach used to induce pancreatitis, namely, noninvasive and invasive models.**

## NONINVASIVE MODELS OF PANCREATITIS

### Secretagogue-Induced Pancreatitis

More than a century ago, Mouret observed that excessive neural stimulation results in injury of the exocrine pancreas. Subsequent studies have not only confirmed these findings but also have shown that in addition to stimulation with the cholinergic agonists (carbamylcholine), excessive stimulation with cholecystokinin (CCK) and its analogue, caerulein, also results in acute pancreatitis. In fact, the caerulein-induced model has become the most widely used model with which to study acute pancreatitis in rodents.

CCK receptors present on the pancreatic acinar cells exist in two affinity states—high and low. Occupancy of high-affinity receptors by low concentrations of CCK (or caerulein) results in stimulation of digestive enzyme secretion, whereas interaction of CCK with low-affinity receptors results in inhibition of digestive enzyme secretion. Acute pancreatitis is induced by occupancy of these low-affinity receptors by caerulein and it can be prevented by administration of CCK-receptor antagonists (e.g., L-364-718 or CCK-JMV-180, an antagonist of low-affinity CCK receptors in rats).

Administration of caerulein to rodents at doses that are 10- to 100-fold higher than those that evoke maximal secretion of digestive enzymes from pancreatic acinar cells results in a rapid development of pancreatitis. Stimulation with supramaximal concentrations of CCK and carbamylcholine can also induce pancreatitis; however, caerulein is used most frequently. Caerulein can be given intravenously at doses sufficient to deliver 5–10 μg/kg/h in a continuous infusion. Alternatively and perhaps more conveniently, pancreatitis can also be induced by hourly intraperitoneal or subcutaneous injections, although this approach is usually not as reliable as intravenous infusions. Pancreatic injury in rats develops rapidly, increases with the duration of infusion, and is maximal within 12 h. This relatively mild form of pancreatitis is characterized by massive pancreatic edema (which can be visualized macroscopically), increased serum levels of pancreatic enzymes (such as amylase and lipase), cytoskeletal (actin) reorganization, acinar cell vacuolization, necrosis, and inflammation. Strikingly, intra-acinar cell activation of trypsinogen can be observed within minutes of initiation of caerulein infusion.

The caerulein-induced model has become the model of choice for studying pancreatitis in mice, particularly in genetically altered strains. For these studies,

 

pancreatitis is usually induced by administration of 8 to 12 hourly intraperitoneal injections of caerulein (50 μg/kg). The resulting pancreatitis is more severe in mice than in rats and after 12 injections of caerulein, the pancreas develops extensive necrosis and inflammation. This noninvasive model has also proved to be a good model with which to study pancreatitis-associated lung injury.

Due to its ease of use and reproducibility, the caerulein-induced model has been extensively used to study the pathophysiological mechanisms involved in pancreatitis. Several recent studies using this model have shown that one of the earliest events in the onset of pancreatitis is the colocalization of digestive enzyme zymogens and lysosomal hydrolases in large vacuoles observed during pancreatitis. This colocalization could result in premature intra-acinar activation of trypsinogen and perhaps other digestive zymogens, leading to acinar cell injury. This model has also been extensively used to elucidate the role of heat shock proteins and inflammatory mediators in pancreatitis and associated lung injury.

Overall, the caerulein-induced model is probably the most popular experimental model of pancreatitis because it offers several advantages: it is very easy and inexpensive to use, is noninvasive, develops rapidly and reproducibly in mice and rats, which are easy to handle and in addition, the severity of the resulting disease can be regulated and manipulated. However, the main drawback of this model is its questionable clinical relevance.

### Diet-Induced Pancreatitis

Administration of ethionine, the ethyl analogue of methionine, was initially shown to induce mild edematous, nonlethal pancreatitis in rats, cats, dogs, and monkeys. Subsequently, Lombardi and co-workers in 1975 developed a model of acute necrotizing hemorrhagic pancreatitis by feeding a choline-deficient ethionine-supplemented (CDE) diet to young female mice. However, this disease is lethal and all the mice die within 5 days if they are fed the CDE diet *ad libitum*. Later, this protocol was modified to reduce the mortality rate to 50 to 70% by limiting diet consumption and feeding the CDE diet for only 24 h. The mice are fasted for 24 h before and after being given the CDE diet. Estrogen and a reduced capacity to neutralize acute pancreatitis enzymes probably mediate the sex difference in response to the dietary regimen.

Like the secretagogue model, this model has also been shown to be associated with a defect in stimulus–secretion coupling and the digestive enzyme zymogens have been shown to be colocalized with the lysosomal enzymes within 1 day of the start of the CDE diet. This model shares many histological and biochemical features with clinical pancreatitis in humans and is also associated with acute lung injury.

### Arginine-Induced Pancreatitis

This infrequently used model, originally described by Tani and co-workers in 1990, involves administration of a single large intraperitoneal injection of L-arginine to rats and results in necrotizing pancreatitis that is less severe than the CDE diet-induced pancreatitis. The disease evolves over a period of 72 h with the initial appearance of small intracellular vesicles within 6 h, a significant elevation in serum amylase and lipase and acinar cell necrosis within 24 h, and a marked inhibition of protein synthesis within 72 h after administration of the injection. Changes in the actin cytoskeleton are an early component in this model of pancreatitis. It is also accompanied by a stress response with a large increase in heat shock proteins 27 and 70. The pancreas starts recovering by 7 days and regains its normal function by 14 days. The mechanism by which L-arginine induces pancreatitis is not well understood although it is likely that it acts by inducing an intracellular stress response.

### Immune-Induced Pancreatitis

Immune-induced pancreatitis can be initiated by a Schwartzmann or an Arthus type of reaction, by injection of foreign serum intraperitoneally or into the pancreatic duct, and by the intraductal injection of anti-pancreatic basement membrane antibodies.

## INVASIVE MODELS OF PANCREATITIS

Observations made as early as 1856 by Claude Bernard and in 1901 by Opie laid the foundation for the development of invasive models of acute pancreatitis. Opie proposed the "common channel" theory on the basis of the autopsy results of two patients who died from acute necrotizing pancreatitis and were found to have gallstones impacted in the ampulla of Vater. According to this theory, the stones obstructed the terminal common channel of the bile and pancreatic ducts so that the bile could now reflux into the pancreatic ductal system and initiate pancreatitis. Although several objections have been raised and alternative hypotheses suggested, this hypothesis is still accepted by many as a valid explanation for the triggering event in gallstone pancreatitis. Alternatively, a stone on passage into the duodenum stretches the sphincter of Oddi, thus permitting reflux of duodenal contents into the pancreatic duct.

Yet another widely accepted theory is based on the premise that obstruction of the pancreatic duct leads to retention of the pancreatic juice within the pancreatic ductal system and that rupture of the intrapancreatic ducts because of the increased ductal pressure leads to spilling of the pancreatic juice containing the digestive enzymes into the gland itself, thereby initiating a cascade of events resulting in pancreatitis.

For the most part, these experimental models have been designed to test the validity of the aforementioned theories and thus include perfusion or retrograde injection of bile and other agents into the pancreatic duct, construction of a closed duodenal loop to facilitate reflux of duodenal contents into the pancreatic ductal system, and temporary obstruction/ligation of the pancreatic or biliopancreatic ductal system.

## Closed Duodenal Loop

This model, one of the first experimental models of acute pancreatitis when it was described by Pfeffer *et al.* in 1957, has undergone a series of modifications over the years and is used mainly to establish the etiology of pancreatitis. In their initial studies, Pfeffer and coworkers, using fasted mongrel dogs, isolated 10 cm of the duodenum just beyond the pylorus and ligated the bile duct so that the closed duodenal segment communicated with the pancreatic ductal system. Gastric outflow was reestablished by construction of a gastrojejunostomy. Under these conditions, edematous changes were noted after 4 h and parenchymal necrosis developed between 9 and 11 h after the surgery. However, fat necrosis and inflammation occurred infrequently. The possible mechanisms of pancreatitis induced using this approach include pancreatic ischemia, overdistension of the duodenal loop, and reflux of the duodenal contents into the pancreatic ductal system since pancreatic duct ligation or pancreatic duct cannulation ameliorates the changes associated with pancreatitis in this model.

The model has undergone several changes including placement of an intralumenal tube in the ligated area to maintain intestinal continuity, performing a gastrojejunostomy and insertion of a bypass cannula (Herrera fistula), and injection of infected bile or bile salt–trypsin mixture into the closed loop.

Since the severity of pancreatitis associated with this model is highly variable and is associated with little or no fat necrosis and inflammation, it is not universally accepted as a model of acute pancreatitis. Furthermore, its clinical relevance still remains to be established.

## Retrograde Ductal Injection and Prograde Perfusion

Acute pancreatitis can be induced in relatively large animals (dogs, cats, pigs, rats) by cannulating the pancreatic duct and retrogradely injecting agents such as activated digestive enzymes (trypsin, elastase, lipase, phospholipase A), bile, bile plus trypsin or the purified bile salt, sodium taurocholate alone or with trypsin, and fatty acids. The critical features of this model are the pressure that is used for injecting these agents and the finding that the severity of pancreatitis is directly correlated with the pressure and the volume of the injected material.

Perhaps the earliest model of acute pancreatitis was developed in 1856 by Claude Bernard, who injected olive oil and bile retrogradely into the pancreatic duct of the dog and observed the subsequent development of pancreatitis. This model is suitable to study the late but not the early events associated with severe pancreatitis. In an attempt to study the early events and to reduce the severity of pancreatitis, Aho and co-workers modified the protocol by injecting small volumes of sodium taurocholate (3 to 5%) over a period of 1 min in rats. The pancreatitis induced in this case evolves slowly over a period of 72 h and the severity of pancreatitis correlates directly with the injected concentration of sodium taurocholate.

Pancreatitis of severity ranging from mild edematous to necrotizing can also be initiated in large animals such as cats, pigs, dogs, and primates by cannulating the pancreatic duct and prograde perfusing it with a permeability-increasing agent at low pressure followed by infusion of infected bile, hydrochloric acid, aspirin, bile salts, or even activated digestive enzymes. Perfusion of the last agent in combination with prostaglandin E2 has been shown to induce necrotizing pancreatitis.

## Duct Ligation/Obstruction Models

Pancreatic duct ligation or obstruction models were designed to recapitulate the events that occur during gallstone pancreatitis in humans. Ligation or temporary obstruction of the pancreatic duct in most animals results in pancreatic edema, mild inflammation, and acinar cell apoptosis, ultimately leading to atrophy of the gland. However, the severity of the pancreatitis can be enhanced by combining duct ligation with stimulation of secretion and pancreatic ischemia. Most of these studies have been performed on rabbits and rats.

On the other hand, ligation of the pancreatic duct or of the common biliopancreatic duct of the American opossum results in severe hemorrhagic pancreatitis, which is associated with acute lung injury and a

14-day mortality rate of 100%. The opossum is a very useful animal for studies mimicking gallstone pancreatitis because its biliopancreatic anatomy closely resembles that of humans. However, unlike in humans where necrotizing pancreatitis is focal and restricted, in the opossum it is diffuse and uniformly distributed throughout the gland. In the opossum, pancreatic duct obstruction appears to be the sole cause of pancreatitis and neither biliary duct obstruction nor bile reflux is essential for triggering or worsening the severity of pancreatitis.

## *IN VITRO* MODEL OF PANCREATITIS

Although pancreatitis is an inflammatory disease, many of the early changes take place in pancreatic acinar cells. For example, in all models of pancreatitis, intra-acinar cell activation of trypsinogen is one of the earliest events that precede overt pancreatitis. In order to study the mechanisms of pathobiological events initiated in pancreatic acinar cells, an *in vitro* model has been developed and has been extensively used in the past few years. In this model, stimulation of rat pancreatic acini with supramaximal concentrations of caerulein results in intra-acinar cell activation of trypsinogen.

For these studies, dispersed pancreatic acini are prepared from freshly harvested pancreas by collagenase digestion and gentle shearing. Acini thus prepared are more than 95% viable and remain healthy for up to 24 h. These acini can be incubated with high concentrations of caerulein and the resulting acinar cell changes can be monitored. Such an *in vitro* reductionist approach has been useful in studies designed to elucidate the mechanisms involved in the activation of trypsinogen and the ensuing acinar cell injury that is observed during pancreatitis. Furthermore, studies using this *in vitro* model have shown that a sustained rise in intracellular calcium is required for activation of trypsinogen and that inhibition of cathepsin B activity prevents this activation.

## CONCLUSIONS

Although a number of models, both invasive and noninvasive, have been developed to study the different aspects of acute pancreatitis, there is still no "perfect model" that recapitulates the events occurring during clinical acute pancreatitis in their entirety. Notwithstanding the shortcomings associated with the models described above, these experimental approaches have helped greatly in unraveling the signaling events and the complex interaction of acinar, nonacinar, and inflammatory cells during the initiation and progression of this disease.

## See Also the Following Article

**Pancreatitis, Acute**

## Further Reading


Aho, H. J., Koskensalo, S. M., and Nevalainen, T. J. (1980). Experimental pancreatitis in the rat. Sodium taurocholate-induced acute haemorrhagic pancreatitis. *Scand. J. Gastroenterol.* 15, 411–414.

Gorelick, F. S., Adler, G., and Kern, H. F. (1993). Cerulein-induced pancreatitis. *In* "The Pancreas: Biology, Pathobiology and Disease" (V. L. W. Go, E. P. DiMagno, J. D. Gardner, E. Lebenthal, H. A. Reber, and G. A. Scheele, eds.), 2nd Ed., pp. 501–526. Raven Press, New York.

Lampel, M., and Kern, H. F. (1977). Acute interstitial pancreatitis in the rat induced by excessive doses of a pancreatic secretagogue. *Virch. Arch. A Pathol. Anat. Histol.* 373, 97–117.

Lerch, M. M., Saluja, A. K., Runzi, M., Dawra, R., Saluja, M., and Steer, M. L. (1993). Pancreatic duct obstruction triggers acute necrotizing pancreatitis in the opossum. *Gastroenterology* 104, 853–861.

Lombardi, B., Estes, J. W., and Longnecker, D. S. (1975). Acute hemorrhagic pancreatitis (massive necrosis) with fat necrosis induced in mice by DL-ethionine fed with a choline-deficient diet. *Am. J. Pathol.* 79, 465–480.

National Digestive Disease Clearinghouse Web Site. Pancreatitis. Available at http://www.niddk.nih.gov/health/digest/pubs/pancreas/pancreas.htm.

Opie, E. L. (1901). The etiology of acute hemorrhagic pancreatitis. *Bull. Johns Hopkins Hosp.* 12, 182–192.

Pfeffer, R. B., Stasior, O., and Hinton, J. W. (1957). The clinical picture of the sequential development of acute hemorrhagic pancreatitis in the dog. *Surg. Forum* 8, 248–251.

Saluja, A. K., Donovan, E. A., Yamanaka, K., Yamaguchi, Y., Hofbauer, B., and Steer, M. L. (1997). Cerulein-induced *in vitro* activation of trypsinogen in rat pancreatic acini is mediated by cathepsin B. *Gastroenterology* 113, 304–310.

Steer, M. L., and Saluja, A. K. (1993). Experimental acute pancreatitis: Studies of the early events that lead to cell injury. *In* "The Pancreas: Biology, Pathobiology and Disease" (V. L. W. Go, E. P. DiMagno, J. D. Gardner, E. Lebenthal, H. A. Reber, and G. A. Scheele, eds.), 2nd Ed., pp. 489–500. Raven Press, New York.

Tani, S., Itoh, H., Okabayashi, Y., Nakamura, T., Fujii, M., Fujisawa, T., Koide, M., and Otsuki, M. (1990). New model of acute necrotizing pancreatitis induced by excessive doses of arginine in rats. *Digest. Dis. Sci.* 35, 367–374.

Williams, J. A. (2001). Intracellular signaling mechanisms activated by cholecystokinin-regulating synthesis and secretion of digestive enzymes in pancreatic acinar cells. *Annu. Rev. Physiol.* 63, 77–97.

# Pancreatitis, Hereditary

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**cationic trypsinogen** Precursor form of trypsin defined by its cationic (net positive) charge.
**hereditary pancreatitis** Form of the disease that appears to be acquired via an inherited gene.
**pancreatitis** Inflammation of the pancreas.

**Hereditary pancreatitis refers specifically to otherwise unexplained acute or chronic pancreatitis in an individual from a family in which pancreatitis appears to be passed down from generation to generation through an inherited gene. Familial pancreatitis is a broader term that refers to pancreatitis of any cause in an individual from a family whose members develop pancreatitis at a higher rate than would be expected by chance alone. Familial pancreatitis may or may not be caused by a genetic mutation. Hereditary pancreatitis therefore defines a narrow, specific term whereas familial pancreatitis is a broad, general term that also encompasses inherited types of pancreatitis.**

## CLINICAL FEATURES

Pancreatitis is inflammation of the pancreas. Acute pancreatitis occurs when normal pancreatic tissue suddenly becomes inflamed. Inflammation is occasionally caused by a bacterial or viral infection or by direct trauma to the abdomen. However, in most cases, acute pancreatitis develops when the inactive pancreatic digestive enzymes become active inside the pancreas rather than inside the intestine. In this case, the pancreas literally begins to digest itself, leading to severe inflammation. Chronic pancreatitis describes the effects of prolonged inflammation in which the normal pancreatic tissue is partially or completely destroyed and replaced with scar tissue.

A typical description of hereditary pancreatitis includes a family history in which the older generations describe lifelong histories of attacks of abdominal pain beginning in childhood. The pain often becomes continuous by adulthood or disappears. In more severe cases, chronic pancreatitis or diabetes mellitus develops, and pancreatic cancer (or an adenocarcinoma of unknown origin) may be seen after age 50 years. In the younger generations, the childhood attacks would be diagnosed as acute pancreatitis. However, only about half of the offspring in each generation develops the typical symptoms, and the other half of the family tree never has symptoms. In some cases, the symptoms skip a generation, demonstrating that about one out of five people with the pancreatitis-causing gene mutation are silent carriers. This pattern of inheritance is typical of autosomal dominant genetic disorders that are passed from generation to generation through a single defective gene.

The average person inheriting a gene mutation causing hereditary pancreatitis has several symptoms. At about age 10 years they begin developing attacks of severe abdominal pain caused by acute pancreatitis. The exact age of first attack in an individual can vary from about 1 year old to adulthood, but usually occurs in childhood. The pain is centered in the epigastrium, which is about a third of the way from the rib cage to the navel. The pain often increases, beginning as a poorly described ache with nausea and becoming a very severe, steady pain with nausea and vomiting. The pain may extend to the back, to the sides (usually left), or to the entire abdomen. It is unusual to have fever or diarrhea, and during the attack the person usually tries to lie in a curled up position and to remain motionless. The attacks may last for 2–3 days (this is also variable), with attacks usually occurring a couple of times a year.

Later in life, about 5–10 years after the first attack of acute pancreatitis, up to half of the individuals with hereditary pancreatitis will develop chronic pancreatitis. The symptoms of chronic pancreatitis include continuous abdominal pain, difficulty digesting food, bulky stools or diarrhea-like symptoms, and (later) diabetes mellitus. Patients with chronic pancreatitis for several decades are also susceptible to pancreatic cancer, especially if they smoke cigarettes.

## CAUSES

The first mutation causing hereditary pancreatitis was discovered in 1996 on chromosome 7 within the *cationic trypsinogen* gene, or *PRSS1*. Trypsinogen is the inactive form of the protein-digesting enzyme trypsin, which

 

cuts protein chains at arginine or lysine amino acids. Trypsinogen normally becomes activated to trypsin after passing into the intestine, and trypsin activates the other inactive digestive enzymes inside the intestine, where ingested food is digested. The hereditary pancreatitis mutation changes the DNA code for a key arginine amino acid (symbol R) at position 122 of the trypsin molecule to code for the amino acid histidine (symbol H), resulting in a "R122H" mutation. Arginine 122 acts an emergency "fail-safe" self-destruction site on the back side of the trypsin molecule, allowing this digestive enzyme to be eliminated by a second trypsin molecule if the trypsinogen becomes active trypsin inside the pancreas. This site is regulated by calcium, and in low calcium concentrations the trypsin will destroy itself (e.g., within the acinar cell). When this site is mutated to histidine, the pancreatic acinar cells cannot eliminate prematurely activated trypsin, which then activates other digestive enzymes. The prematurely active digestive enzymes begin digesting the pancreas, leading to acute pancreatitis. Repeated episodes of acute pancreatitis lead to severe scarring of the pancreas, or chronic pancreatitis. About two-thirds of the families with hereditary pancreatitis have one of several known cationic trypsin mutations, and the other third has unknown mutations.

## DIAGNOSIS AND TREATMENT

The diagnosis of hereditary pancreatitis is currently made by diagnosing pancreatitis in two or more members of a family in two generations in which other causes have been excluded (for example, pancreatitis from gallstones). In addition, hereditary pancreatitis can be diagnosed in individuals with pancreatitis through genetic testing. The two common mutations for which testing is recommended are the cationic trypsinogen R122H and N21I mutations. Mutations in the trypsin inhibitor gene (*SPINK1*) and some mutations in the cystic fibrosis gene (*CFTR*) are also seen in pancreatitis, but usually not in families with hereditary pancreatitis. Mutations in these genes are common, and a single mutation does not cause the pancreatitis seen in hereditary pancreatitis.

Currently, there are no specific, proved therapies to prevent or treat hereditary pancreatitis. Smaller meals, diets low in fat and protein, and vitamin and antioxidant supplements have been recommended by some experts, and are usually not discouraged. Smoking cigarettes and alcohol consumption are strongly discouraged because these factors promote pancreatitis and contribute to pancreatic cancer. Medications to reduce stomach acid, supplements containing pancreatic enzymes, and even insulin injections may be necessary if chronic pancreatitis develops. Surgery may be necessary to treat some complications.

## See Also the Following Articles

**Diabetes Mellitus • Pancreatic Cancer • Pancreatitis, Acute • Pancreatitis, Chronic • Trypsin**

## Further Reading

Ellis, I., Lerch, M. M., and Whitcomb, D. C. (2001). Consensus committees. Genetic testing for hereditary pancreatitis: Guidelines for indications, counseling, consent and privacy issues. *Pancreatology* 1(5), 405–418.

Etemad, B., and Whitcomb, D. C. (2001). Chronic pancreatitis: Diagnosis, classification, and new genetic developments. *Gastroenterology* 120, 682–707.

Lowenfels, A. B., Maisonneuve, P., Whitcomb, D. C., Lerch, M. M., and DiMagno, E. P. (2001). Cigarette smoking as a risk factor for pancreatic cancer in patients with hereditary pancreatitis. *J. Am. Med. Assoc.* 286(2), 169–170.

Whitcomb, D. C. (2002). Hereditary diseases of the pancreas. *In* "Textbook of Gastroenterology" (T. Yamada, D. H. Alpers, L. Laine, C., Kaplowitz, N., Owyang, and D. W. Powell, eds., 4th Ed., pp. 2147–2165. Lippincott Williams & Wilkins, Philadelphia.

Whitcomb, D. C., Gorry, M. C., Preston, R. A., Furey, W., Sossenheimer, M. J., Ulrich, C. D., *et al.* (1996). Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene. *Nat. Genet.* 14(2), 141–145.

# Pancreatitis, Pediatric

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**acute pancreatitis** An acute inflammatory condition of the pancreas associated with a broad variety of etiologies in children.

**chronic pancreatitis** An inflammatory condition of the pancreas with evidence of permanent and progressive morphological damage.

**hereditary pancreatitis** An autosomal dominant disease that accounts for 1% of cases of both chronic and recurrent pancreatitis; genetic mutations have been identified in cationic trypsinogen for many patients.

**metabolic pancreatitis** Pancreatic disorder related to abnormalities such as hyperlipidemia or hypercalcemia, which can cause acute or recurrent pancreatitis but which is extremely rare in pediatrics.

**pseudocyst** A complication of pancreatitis with a cystic structure not lined with epithelium, which distinguishes it from a true cyst. Most commonly, the walls of the cyst are formed in part by the stomach, spleen, and pancreas.

**sphincterotomy** Incision of the sphincter of Oddi (with reference to pancreatitis).

**Pancreatic disorders in childhood include congenital anatomic and genetic disorders as well as acquired disorders. Most of these disorders are rare. This article will focus on the various types of pancreatitis and briefly describe their clinical characteristics.**

## ACUTE PANCREATITIS

Acute pancreatitis is an acute inflammatory condition of the pancreas. It is associated with a broad variety of causes in childhood, in contrast to the two main causes of gallstones and alcohol in adults (Table I). Nearly 20% of pediatric cases of pancreatitis are associated with trauma, approximately 10% are associated with gallstones or congenital structural abnormalities of the pancreatico-biliary ductular system, and less than 5% are associated with medications; only rarely are cases associated with metabolic abnormalities and between 15 and 20% have no explanation even after exhaustive evaluation (idiopathic). Over half of all children with pancreatitis have an associated systemic illness. Of those with multisystem disease, between one-quarter and one-third present with sepsis or shock, approximately 5% have an associated viral illness, and over half have a systemic illness, such as a collagen vascular disease or heart disease. In children under 4

**TABLE I Reported Causes of Acquired Pancreatitis in Children**

| |
|---|
| Trauma |
| Biliary tract disease |
| Gallstones |
| Structural abnormalities (e.g., choledochal cyst) |
| Drug-induced |
| Azathioprine |
| Valproic acid |
| L-Asparaginase |
| Thiazides |
| Tetracyclines |
| Sulfonamides |
| Furosemide |
| Estrogen |
| Infection |
| Mumps virus (uncommon now) |
| Enterovirus |
| Epstein–Barr virus |
| Hepatitis A virus |
| Coxsackie virus B |
| Influenza A |
| Measles (uncommon now) |
| Leptospirosis |
| Mycoplasmosis |
| Typhoid fever |
| Ascariasis |
| Malaria |
| Rubella (uncommon now) |
| Metabolic |
| Protein-calorie malnutrition |
| Hypercalcemia |
| Reye's syndrome (rare now) |
| Hypertriglyceridemia |
| Cystic fibrosis (pancreatic sufficiency) |
| Miscellaneous |
| Henoch-Schönlein purpura |
| Systemic lupus erythematosus |
| Perforated duodenal ulcer |
| Kawasaki disease |
| Congenital partial lipodystrophy |
| Juvenile tropical pancreatitis |
| Following endoscopic retrograde cholangiopancreatography |

years of age, the final diagnosis is rarely idiopathic, and in children under 3 years of age, all patients will have an associated systemic illness, such as sepsis or shock.

The incidence of pancreatitis in childhood has been difficult to determine. Acute pancreatitis has been an uncommon diagnosis at most pediatric institutions. However, a recent single institution review suggested that there may be an increasing incidence with between 70 and 100 new cases of pancreatitis now identified each year. The symptoms at presentation are similar to those in adults. Typically, children present with abdominal pain and/or vomiting. The combination of elevated serum lipase and amylase levels is reliable for the diagnosis of pancreatitis in children. Pancreatitis appears to be less severe in children with a low mortality compared to adults (no prospective studies available). However, severe metabolic and physical complications, such as hypoalbuminemia, hypocalcemia, pseudocysts, necrosis, pleural effusions, and hypoxia, can result.

Hemorrhagic pancreatitis is said to occur in approximately 13% of cases, but in recent experience it appears to be less frequent. Use of Ranson's or the Glasgow criteria to assess severity has not been validated for the pediatric population, but these criteria appear to be useful in providing evidence of complications.

Pseudocysts are reported to occur in approximately 15% of children with pancreatitis but limited information about this complication is available. Usually, the amylase and lipase levels are elevated and associated with abdominal pain, emesis, and/or fever.

The mainstay of treatment is symptomatic and similar to that in adults.

## CHRONIC PANCREATITIS

Chronic pancreatitis is an inflammatory condition of the pancreas with evidence of permanent and progressive morphological damage observed on biopsy, autopsy, or radiological studies. Clinically, it is characterized by recurrent or persistent abdominal pain (80% of patients). Steatorrhea and weight loss may also be present. The incidence and prevalence of this condition in children are uncertain but chronic pancreatitis is uncommon. However, estimates in adults suggest that the prevalence is between 1 and 5% with an incidence of close to 8 cases per 100,000 population.

In children, chronic pancreatitis appears to result in two primary forms: (1) a calcifying form that can be associated with hereditary pancreatitis, hypercalcemia, hyperlipidemia, cystic fibrosis (with pancreatic sufficiency), juvenile tropical pancreatitis, and idiopathic pancreatitis and (2) an obstructive form (unusual in children) that is more commonly associated with trauma, sclerosing cholangitis, sphincter of Oddi dysfunction, congenital anomalies, idiopathic fibrosing pancreatitis, and chronic renal failure. Autoimmune pancreatitis resulting in chronic pancreatitis has been described in adults but, as of this writing, it has not been recognized in children.

Genetic susceptibility to chronic pancreatitis appears to be related to mutations in the cationic trypsinogen gene (PRSS1; see Hereditary Pancreatitis below), cystic fibrosis transmembrane conductance regulator (CFTR), and polymorphisms in the serine protease inhibitor, Kazal type 1 (SPINK1). These mutations do not account for all cases of chronic pancreatitis.

Treatment is symptomatic and similar to that used in adults.

## HEREDITARY PANCREATITIS

Hereditary pancreatitis is an autosomal dominant disease that accounts for 1% of cases of both chronic and recurrent pancreatitis. The disease has been associated with mutations in the cationic trypsinogen gene. In addition, polymorphisms in SPINK 1 appear to increase the risk for the development of both familial (hereditary) and chronic pancreatitis but not primarily cause it. Clinically, there is incomplete penetrance with variability in the age at presentation and the severity of symptoms. Symptoms can begin as early as the first decade and are present in up to 80% of affected individuals by 20 years of age (range between 11 months and old age). Initial attacks resemble those of acute pancreatitis. Over time, patients develop signs and symptoms more typical of chronic pancreatitis although some patients will have calcification and some evidence of atrophy at the time of first presentation.

If hereditary pancreatitis evolves to chronic pancreatitis, some patients will develop complications more typical of this chronic disorder, including fibrosis, ductal abnormalities, calcifications, diabetes mellitus (reported in 10–25% of cases), steatorrhea and malabsorption (reported in 5 to 45% of cases), pseudocysts, and portal and splenic vein thrombosis. A more serious complication is that of pancreatic cancer, which may have a greater than 50-fold increased incidence in patients with hereditary pancreatitis.

Therapeutic interventions remain symptomatic. Thus, the approaches used are the same as those for other forms of pancreatic inflammation. Additionally, antioxidant cocktails are commonly prescribed. There are limited data supporting their effectiveness in this condition, although they are reported to be effective in recurrent pancreatitis.

## METABOLIC PANCREATITIS

### Hyperlipidemia

Hyperlipidemia is a reported cause of pancreatitis but appears to be exceedingly rare in pediatrics. The reported incidence of pancreatitis for each type of hyperlipidemia is as follows: type I, 35%; type IV, 15%; and type V, 30–40%. The pancreatitis appears to be acute and recurrent. Use of an antioxidant cocktail has been reported to stop recurrent episodes of pancreatitis related to hyperlipidemia. If triglycerides are elevated during an episode of acute pancreatitis, they should be reevaluated after resolution of the pancreatitis to determine whether an underlying error in lipid metabolism is present.

### Hypercalcemia

Hypercalcemia is a rare cause of pancreatitis. It can result from a variety of disorders, including total parenteral nutrition, vitamin D poisoning, sarcoidosis, metastatic bone disease, and the infusion (iatrogenic) of high doses of calcium. The role of primary hyperparathyroidism in either acute or chronic pancreatitis is unclear but certainly is a rare cause. It appears to occur in 7–15% of all patients with hyperparathyroidism and accounts for less than 1% of all cases of pancreatitis in adults or children.

## See Also the Following Articles

**Hyperlipidemia • Pancreatic Disease, Pediatric • Pancreatitis, Acute • Pancreatitis, Chronic • Pancreatitis, Hereditary**

## Further Reading

Digmagno, E. P., and Chari, S. (2002). Acute pancreatitis. *In* "Slesinger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, Management" (M. Feldman, L. S. Friedman, and M. H. Sleisenger, eds.), 7th Ed., pp. 913–941. W. B. Saunders, New York.

Etemad, B., and Whitcomb, D. C. (2001). Chronic pancreatitis: Diagnosis, classification, and new genetic developments. *Gastroenterology* 120, 682–707.

Forsmark, C. E. (2002). Chronic pancreatitis. *In* "Slesinger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, Management" (M. Feldman, L. S. Friedman, and M. H. Sleisenger, eds.), 7th Ed., pp. 943–969. W. B. Saunders, New York.

Lopez, M. J. (2002). An increasing incidence of acute pancreatitis: A single institution perspective. *J. Pediatr.* 140, 622–624.

On-line Mendelian Inheritance in Man web site. Available at http://www.ncbi.nlm.nih.gov/Omim/. [See entries for No. 167800, Pancreatitis, Hereditary; No. 276000, Protease, Serine, 1 (cationic trypsinogen); and No. 167790, Serine Protease Inhibitor, Kazal-Type, 1; Spink1].

Whitcomb, D. C. (2002). Hereditary and childhood disorders of the pancreas, including cystic fibrosis. *In* "Slesinger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, Management" (M. Feldman, L. S. Friedman, and M. H. Sleisenger, eds.), 7th Ed., pp. 881–912. W. B. Saunders, New York.

# Paraneoplastic Syndrome

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**chronic intestinal pseudo-obstruction** A syndrome due to a failure of intestinal propulsion and characterized by a clinical picture resembling mechanical obstruction in the absence of any lesion occluding the lumen of the gut.

**enteric nervous system** The collection of neurons embedded in the wall of the gastrointestinal tract, organized in two major ganglionated (i.e., the myenteric or Auerbach's and submucosal or Meissner's) plexuses and able to control all digestive functions, including motility, absorption/secretion, sensitivity, and microcirculation.

**onco-neural antigens** Antigens shared by tumor cells and neural tissues that are likely capable of triggering the immune response involved in the neuropathophysiology of paraneoplastic syndrome.

**Paraneoplastic syndromes encompass a wide array of clinical manifestations that may affect virtually all organs of the human body as a result of a systemic response evoked by a remote tumor. The gastrointestinal tract may be the target of a paraneoplastic syndrome evoked most commonly by small-cell lung carcinoma, thymoma, and gynecological and breast tumors. Symptoms arising in this context include diarrhea, constipation, nausea, vomiting, and abdominal pain. These symptoms may precede the diagnosis of the underlying neoplastic disease; thus, the differential diagnosis of gastrointestinal manifestations may also take into account the occurrence of a remote cancer. Symptoms are the result of altered gastrointestinal secretory motor function related to an impairment of the intrinsic innervation supplying the gastrointestinal tract (i.e., the enteric nervous system).**

## INTRODUCTION AND GENERAL FEATURES

Certain types of tumors express molecules, namely, onco-neural antigens, against which the immune system reacts as part of the immune-mediated anti-neoplastic response. This humoral and cell-mediated immune response cross-reacts with onco-neural antigens physiologically expressed by the enteric nervous system, thus leading to dysfunction and structural damage. As a result, a severe perturbation of gastrointestinal motility, ranging from achalasia, gastroparesis, and megacolon to chronic intestinal pseudo-obstruction, occurs. The histopathological hallmark of these motor disorders is an inflammatory lympho-plasmacellular infiltrate within the ganglionated plexuses of the enteric nervous system, mainly in the myenteric plexus (or Auerbach's plexus). This histopathological picture, referred to as myenteric ganglionitis, is associated with degeneration and loss of neurons, likely reflecting the immune-mediated injury within the myenteric plexus, throughout the gastrointestinal tract.

## TYPES OF ANTI-NEURONAL ANTIBODIES IN PARANEOPLASTIC SYNDROME

In addition to a cellular immune response, several distinctive anti-neuronal antibodies can be found in the serum of patients with paraneoplastic dysmotility. Depending on their molecular target, they are referred to as anti-Hu (also known as type 1 anti-neuronal nuclear antibodies), anti-Yo (anti-Purkinje cell cytoplasmic antibodies), P/Q- and N-type $Ca^{2+}$ channel antibodies, and ganglionic-type nicotinic acetylcholine receptor antibodies. Although the pathogenetic role played by anti-neuronal antibodies in enteric neuronal damage is still under investigation, their detection is of great importance in the diagnosis of an underlying, often occult, tumor.

Anti-Hu antibodies, usually found in the serum of patients with paraneoplastic encephalomyelitis/subacute sensory neuropathy, can be also detected in paraneoplastic gastrointestinal dysmotility. The Hu antigens are four nervous system-specific RNA-binding proteins, with a crucial role in neuronal development and survival. It is plausible that binding of autoantibodies to the enteric neuronal Hu proteins may play a role in the neuronal dysfunction underlying gastrointestinal paraneoplastic syndrome. Another class of anti-neuronal antibodies includes the anti-voltage-gated

 

$Ca^{2-}$ channels, which are often identified in the serum of patients with Lambert-Eaton myasthenic syndrome associated with small-cell lung carcinoma. These autoantibodies, including the P/Q- and N-type $Ca^{2-}$ channels (which control acetylcholine release), may also be involved in central as well as autonomic nervous system dysfunction related to paraneoplastic syndromes. Together with anti-Hu antibodies, the N-type anti-voltage-gated $Ca^{2+}$ channel antibodies are the most common autoantibodies described in patients with paraneoplastic dysmotility.

Anti-Yo antibodies, found in the serum of patients with paraneoplastic cerebellar degeneration as a manifestation of gynecologic or breast cancer, are also detected in rare cases of paraneoplastic gastrointestinal dysmotility related to ovarian carcinoma. These antibodies target the Yo (recently redefined as cerebellar degeneration-related) antigens, which exert a functional inhibition of c-*myc* transcriptional activity, likely inducing neuronal damage through the activation of apoptosis.

In severe gastrointestinal dysmotility, the suspicion of a paraneoplastic syndrome should be always taken into account. Testing for neuronal autoantibodies is helpful for accurate diagnosis of patients with paraneoplastic syndrome. Further research is needed to better clarify the mechanisms underlying paraneoplastic-related enteric neuropathy.

## See Also the Following Articles

**Enteric Nervous System • Gastric Motility • Intestinal Pseudoobstruction**

## Further Reading

De Giorgio, R., Stanghellini, V., Barbara, G., Corinaldesi, R., De Ponti, F., Tonini, M., Bassotti, G., and Sternini, C. (2000). Primary enteric neuropathies underlying gastrointestinal motor dysfunction. *Scand. J. Gastroenterol.* 35, 114–122.

Krishnamurthy, S., and Schuffler, M. D. (1987). Pathology of neuromuscular disorders of the small intestine and colon. *Gastroenterology* 93, 610–639.

Lennon, V. A. (1996). Calcium channel and related paraneoplastic disease autoantibodies. *In* "Textbook of Autoantibodies" (J. B. Peter, and Y. Shoenfeld, eds.), pp. 139–147. Elsevier Science, Amsterdam, The Netherlands.

Musunuru, K., and Darnell, R. B. (2001). Paraneoplastic neurologic disease antigens: RNA-binding proteins and signaling proteins in neuronal degeneration. *Annu. Rev. Neurosci.* 24, 239–262.

Sutton, I., and Winer, J. B. (2002). The immunopathogenesis of paraneoplastic neurological syndromes. *Clin. Sci.* 102, 475–486.

# Parasitic Diseases, Overview

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cyst An environmentally stable form of the life cycle of a protozoan that reproduces asexually. The cyst has a hard outer wall and is involved in the transmission of the organism from one host to another.

definitive host The host in which a parasite achieves sexual maturity.

intermediate host For a parasite with sexual reproduction, this is an additional host(s) in which a parasite develops to some extent, but not to sexual maturity.

oocyst Cystic stage of the Apicomplexa, resulting from sporogony (e.g., *Plasmodium*, *Cryptosporidium*, *Toxoplasma*, *Cyclospora*).

parasite An organism that is physiologically dependent on another organism and extracts its nutrients from this host. More specifically, when the term is used for organisms colonizing humans, it frequently refers to protozoans and helminths and sometimes ectoparasites (e.g., ticks, lice).

trophozoite The vegetative or growing form of an organism, used to describe an asexual stage of a protozoan organism.

**All the noncommensal (and perhaps commensal) bacteria, fungi, protozoa (or protists), and helminths are parasitic organisms when they colonize their human hosts. However, this article will be limited to the more commonly used, narrow definition that includes only the protozoa and helminths. The parasitic diseases are major causes of morbidity and mortality throughout the world, but strike the populations of the tropical and developing regions disproportionately. *Plasmodium falciparum*, the species that causes most cases of fatal malaria, along with *Mycobacterium tuberculosis*, is one of the two organisms most likely to cause fatal infection. Substantial disease burden also results from numerous other protozoan and helminthic organisms. This article will focus primarily on those parasitic organisms that cause diseases with significant gastrointestinal manifestations.**

## INTRODUCTION

In addition to the readily apparent differences in biology and size of the protozoa in comparison to the helminths, there are a number of important generalizations that can be made in regard to the differences in human infections and clinical manifestations. All of the protozoa that are pathogenic for humans are microscopic unicellular organisms that have the ability to reproduce asexually within the human host and thus have the potential to cause a very high disease burden from a single inoculating organism. In contrast, the pathogenic helminths are multicellular organisms that replicate sexually in the definitive host and many require at least one intermediate host to complete their life cycles. Therefore, they do not multiply within the human host, so the disease manifestations are determined by the initial inoculum size, the chronicity, and the host response to the infection. Most of the helminths do not live in the human host for more than several years, so late clinical manifestations are generally the residual of earlier infection and inflammatory response rather than ongoing infection. A corollary of this principle is that acquired immunodeficiency syndrome (AIDS) and other forms of immunocompromise do not result in the markedly increased disease burden that can be seen with protozoa, fungi, or bacteria. The major exception to this general rule is *Strongyloides stercoralis*, which has an autoinfection cycle and is able to replicate to very high numbers in immunocompromised human hosts, especially those receiving high doses of corticosteroids.

Blood eosinophilia is common with invasive helminth infections, frequently reaching very high levels (e.g., 30 to 50% of cases). The degree of eosinophilia is relatively mild in helminths that reside in the gut lumen. Protozoan pathogens typically do not evoke significant blood eosinophilia, but *Entamoeba histolytica* infections do frequently cause tissue eosinophilia. The most common (and not so common) medically important protozoa are listed in Table I and the helminths are listed in Table II. The subsequent portion of this article will give a brief description of the parasites with significant gastrointestinal manifestations. Even for those organisms without significant gastrointestinal manifestations, the diagnosis may be established by identification of the organism or its eggs in intestinal or fecal samples. The organisms for which the diagnosis may be made by gastrointestinal samples are listed in Table III.

 

**TABLE 1 Protozoa Pathogenic for Humans**

| Organism | Classification | Geographic distribution | Means of human acquisition | Other mammalian hosts | Tissue tropism | Method of diagnosis | Clinical manifestations |
|---|---|---|---|---|---|---|---|
| *Plasmodium* sp. | Apicocomplexa (Sporozoa) | Tropical and subtropical regions | Anopheline mosquito bite | None (for human *Plasmodium* species) | Erythrocytes | Microscopic examination of blood smear | Febrile illness |
| *Babesia* spp. | Apicocomplexa | Worldwide | Tick bite | Rodent (*B. microti*); cattle (*B. bovis* and *B. divergens*) | Erythrocytes | Microscopic examination of blood smear | Febrile illess |
| *Toxoplasma gondii* | Apicocomplexa | Worldwide | Ingestion of pseudocysts in contaminated meat; ingestion of oocysts in material contaminated by cat feces; vertical transmission | Cat is definitive host; numerous mammals are incidental hosts | Nucleated cells, especially in heart and brain | Histology; serology | Multiple |
| *Cryptosporidium parvum* | Apicocomplexa | Worldwide | Ingestion of oocysts, especially in contaminated water | Cattle and other mammals | Small intestinal epithelial cells | Stool microscopy; intestinal histology | Diarrhea; rare extraintestinal disease |
| *Cyclospora cayetanensis* | Apicocomplexa | Worldwide | Ingestion of oocysts in contaminated food or water | None known | Small intestine | Stool microscopy | Diarrhea |
| *Sarcocystis* sp. | Apicocomplexa | Worldwide, especially Southeast Asia | Ingestion of sporocysts from feces or meat (human is definitive host); ingestion of fecal oocysts (human is intermediate host) | Carnivore is definitive host; herbivore is intermediate host | Muscle cells | Histology (muscle) | Usually asymptomatic; myositis; diarrhea |
| *Isospora belli* | Apicocomplexa | Tropical and subtropical regions | Ingestion of oocyst | None known | Small intestine | Stool microscopy | Diarrhea |
| *Leishmania* sp. | Kinetoplastid flagellate | Different locales for different species in tropical and subtropical regions | Bite of sandfly | Numerous | Histology; serology (for visceral) | Visceral infection; mucocutaneous; cutaneous | |
| *Trypanosoma cruzi* | Kinetoplastid flagellate | South and Central America | Bite of Reduvid bug | Numerous | Muscle, especially cardiac and GI | Serology | Acute (meningitis or carditis); chronic (cardiomyopathy, mega-GI disease) |
| *Trypanosoma brucei* sp. | Kinetoplastid flagellate | Equatorial Africa | Bite of Tsetse fly | Game animals (East African); none (West African) | Lymphatics, blood; CNS | Microscopy of blood or CSF; Histology | Febrile illness with lymphadenopathy, meningoencephalitis |

(continues)

**TABLE 1 Protozoa Pathogenic for Humans (*continued*)**

| Organism | Classification | Geographic distribution | Means of human acquisition | Other mammalian hosts | Tissue tropism | Method of diagnosis | Clinical manifestations |
|---|---|---|---|---|---|---|---|
| *Giardia lamblia* | Diplomonad flagellate | Worldwide | Ingestion, most commonly through contaminated water | Numerous | Small intestine | Stool microscopy; stool antigen detection | Diarrhea; malabsorption |
| *Entamoeba histolytica* | Rhizopod (ameba) | Developing regions | Ingestion, most commonly through contaminted food | None | Stool microscopy; serology | Colitis; hepatitic "abscesses" | |
| *Dientamoeba fragilis* | Trichomonad | Worldwide | Water: fecal–oral | | Intestine | Stool microscopy | Usually asymptomatic; diarrhea |
| *Balantidium coli* | Ciliate | Worldwide | Ingestion of cysts | Numerous, especially pigs | Colon | Stool microscopy; intestinal histology | Usually asymptomatic; colitis |
| *Blastocystis hominis* | Unknown | Worldwide, especially developing regions | Probably fecal–oral | Unknown | Intestine | Stool microscopy | Usually asymptomatic; may cause diarrhea |
| *Naegleria fowleri* | Rhizopod (ameba) | Warm climate; freshwater | Nasal invasion from swimming in warm freshwater | Free living | CNS | Microscopy of CSF | Meningitis |
| *Acanthamoeba* spp. | Rhizopod (ameba) | Worldwide | Eye (direct contact) | Free-living | CNS; cornea | CNS (brain histology); eye (histology or culture) | Meningoencephalitis; keratitis |
| *Trichomonas vaginalis* | Trichomonad | Worldwide | Sexual | None | Vaginal epithelium | Microscopy of vaginal fluid | Vaginitis |
| *Enterocytozoon bieneusi* | Microsporidia | Worldwide | Ingestion of contaminated water | Numerous | Gastrointestinal tract | Stool microscopy | Diarrhea (chronic in AIDS) |

TABLE II Helminths Pathogenic for Humans

| Organism | Geographic distribution | Means of human acquisition | Definitive host | Intermediate host(s) | Tissue tropism | Method of diagnosis |
|---|---|---|---|---|---|---|
| **Nematodes** | | | | | | |
| *Ascaris lumbricoides* | Worldwide, especially tropics | Egg ingestion | Human, possibly other mammals | None | Small intestine | Identify ova in stool |
| *Ancylostoma duodenale* (Old World hookworm) | Eastern hemisphere | Penetration of skin by larvae | Human | None | Small intestine | Identify ova in stool |
| *Necator americanus* (New World hookworm) | Americas | Penetration of skin by larvae | Human | None | Small intestine | Identify ova in stool |
| *Enterobius vermicularis* | Worldwide | Egg ingestion | Human | None | Cecum | Identify worms in perianal area |
| *Trichuris trichiura* | Worldwide, especially developing regions | Egg ingestion | Human, other mammals | None | Large intestine | Identify ova in stool |
| *Trichinella spiralis* | Worldwide | Ingestion of larvae from muscle | Numerous carnivores | Same as definitive | Small intestine, muscle | Serology, identify larvae in muscle |
| *Wuchereria bancrofti* | Tropics and subtropics | Larvae injected by mosquito | Human | Mosquito | Blood, lymphatics | Identify microfilariae in blood, serology |
| *Brugia malayi* | South and Southeast Asia | Larvae injected by mosquito | Human | Mosquito | Blood, lymphatics | Identify microfilariae in blood, serology |
| *Onchocerca volvulus* | Africa, Central and South America | Larvae injected by blackfly | Human | Blackfly | Eye, skin | Identify microfilariae in skin, serology |
| *Strongyloides stercoralis* | Worldwide, especially tropics and subtropics | Penetration of skin by larvae; Penetration of colon by larvae (autoinfective cycle) | Human (also free-living) | None | Small intestine | Identify larvae in concentrated fecal samples, serology |
| **Trematodes** | | | | | | |
| *Schistosoma mansoni* | Africa, South America | Penetration of skin by cercariae | Human | Snail | Inferior mesenteric veins | Identify eggs in stool, serology |
| *Schistosoma hematobium* | Africa, Middle East | Penetration of skin by cercariae | Human | Snail | Vesical plexus | Identify eggs in urine |
| *Schistosoma japonicum* | Southeast Asia | Penetration of skin by cercariae | Human | Snail | Superior mesenteric veins | Identify eggs in stool, serology |
| *Paragonimus westermani* | Asia, Africa, South America | Ingestion of metacercariae | Human | Snail, crab | Lungs | Identify eggs in stool |
| *Clonorchis sinensis* | Southeast Asia | Ingestion of metacercariae | Human | Snail, fish | Biliary system | Identify eggs in concentrated stool |
| *Fasciola hepatica* | Sheep-raising areas | Ingestion of metacercariae | Human | Snail, watercress | Billary system | Identify eggs in stool |
| **Cestodes** | | | | | | |
| *Taenia solium* | Scattered worldwide | Ingestion of cysticerci in meat (to be definitive host); ingestion of eggs (to be intermediate host) | Human | Pigs (occasionally humans) | Intestine (muscle and brain as intermediate host) | Identify eggs or proglottids in stool, serology |
| *Taenia saginata* | Cattle-raising areas | Ingestion of cysticerci in meat | Human | Cattle | Intestine | Identify eggs or proglottids in stool |
| *Echinococcus* spp. | Scattered worldwide | Egg ingestion | Canines | Numerous mammals | Liver, other organs | Serology, identify cysts in lesions |
| *Diphyllobothrium latum* | Scattered worldwide | Cyst ingestion from uncooked fish | Human, other mammals | Freshwater fish | Intestine | Identify eggs or proglottids in stool |

TABLE III Important Parasitic Infections Diagnosed from Gastrointestinal Samples

| Organism | Type of sample |
|---|---|
| Protozoa | |
| *Entamoeba histolytica* | Identification of cysts or trophozoites in feces or colon biopsy specimens (also do serology) |
| *Giardia lamblia* | Identification of cysts or trophozoites in feces |
| *Cryptosporidium parvum* | Identification of oocysts in feces or merozoites in intestinal biopsies |
| *Cyclospora cayetanensis* | Identification of oocysts in feces |
| *Isospora belli* | Identification of oocysts in feces |
| *Enterocytozoon bieneusi* | Identification of organism in intestinal biopsy or fecal sample |
| Helminths | |
| *Trichuris trichiura* | Identification of ova in microscopic examination of stool |
| *Enterobius vermicularis* | Identification of pinworms in perianal region |
| *Ascaris lumbricoides* | Identification of ova in microscopic examination of stool |
| *Strongyloides stercoralis* | Identification of larvae in feces or duodenal contents; poor sensitivity, so serologic studies should also be performed |
| Hookworm (*N. americanus* and *A. duodenale*) | Identification of ova in microscopic examination of stool |
| *Schistosoma mansoni* | Identification of ova in feces or rectal biopsy; serologic studies are helpful |
| *Clonorchis sinensis* | Identification of ova in feces using concentration techniques |
| *Fasciola hepatica* | Identification of ova or adult worms in feces |
| *Paragonimus westermani* | Identification of ova in microscopic examination of stool |
| *Taenia solium* | Identification of parasite proglottids or ova in feces (ova appear identical to *T. saginata* ova) |
| *Taenia saginata* | Identification of parasite proglottids or ova in feces (ova appear identical to *T. solium* ova) |
| *Diphyllobothrium latum* | Identification of parasite proglottids or ova in feces |

## PROTOZOA

The protozoa have generally been classified according to morphologic criteria into four major groups, the Sporozoa, the flagellates, the amebas, and the ciliates. The Sporozoa form a diverse group of organisms in terms of their hosts, transmission cycles, tissue tropism, and clinical manifestations, but clearly fall into one clade or genetic group. In contrast, the flagellates form several genetic groupings: the kinetoplasts (*Trypanosoma* spp., *Leishmania* spp.), the diplomonads (*Giardia lamblia*), and the trichomonads (*Trichomonas vaginalis*). *En. histolytica* is the most important pathogen of the amebas. *Balantidium coli* is rarely a pathogen, but is frequently listed since it is the only medically important ciliate. In addition to these four groups, the microsporidia have emerged as important pathogens, especially as complications of human immunodeficiency virus (HIV) infection. The microsporidia may actually be fungi, but will be addressed here since they are commonly considered to be protozoa. In addition to the pathogenic organisms, a number of protozoa are frequently identified in fecal specimens, but are seldom or never associated with disease. *Blastocystis hominis* may occasionally be pathogenic, although this remains controversial. *Entamoeba coli*, *Entamoeba hartmanni*, and *Endolimax nana*, as well as a number of other organisms, may be identified in fecal specimens, but are nonpathogenic.

*En. histolytica* is the most frequent parasitic cause of life-threatening gastrointestinal disease, resulting in an estimated 100,000 deaths per year throughout the world. Human infection is initiated by ingestion of *En. histolytica* cysts via contaminated food or water or by direct contact with infected individuals. There are no known nonhuman hosts, so zoonotic transmission does not occur. An accumulation of literature since 1978 has provided convincing evidence of pathogenic and nonpathogenic strains of *En. histolytica*, eventually resulting in the division of these organisms into two species, the pathogenic *En. histolytica* and the nonpathogenic *En. dispar*. The two organisms appear the same morphologically, so routine fecal specimens will not distinguish between the two.

After excystation in the small intestine, *En. histolytica* trophozoites replicate in the large intestine, where they ingest host immune cells and erythrocytes and cause tissue necrosis. Infected patients have locally invasive disease with abdominal pain, bloody diarrhea, and fever. Occasionally, the trophozoites disseminate beyond the large intestine, most commonly to the

liver. Patients with liver involvement have right upper quadrant abdominal pain and fever and discrete lesions that can be identified by ultrasound or computed tomography (CT) scanning. The finding of liver abscesses in a patient with a compatible clinical presentation who has anti-amebic antibodies is nearly diagnostic of amebic liver abscess, but pyogenic liver abscesses should be ruled out in patients with negative serologic tests and those who fail to respond to appropriate medical therapy (usually metronidazole).

Although the observation of *Entamoeba* cysts in fecal specimens in fecal specimens will not distinguish between *En. histolytica* and *En. dispar* infections, the discovery of trophozoites engulfing red blood cells (RBCs) is diagnostic of *En. histolytica* infection. RBCs are commonly present in stool specimens, but white blood cells are uncommon, probably because the trophozoites ingest the neutrophils. In invasive colonic disease, an antibody response is found in over 90% of patients. Although these are not protective antibodies, their measurement is very useful in the diagnosis of amebiasis. Up to 99% of patients with extraintestinal amebiasis will demonstrate an antibody response.

*G. lamblia* is a common cause of diarrheal disease with malnutrition and weight loss throughout the world. Human infection is initiated when the environmentally stable cysts are ingested, most commonly via contaminated water or by direct fecal–oral contact, such as may occur in a day-care center. Although there has been considerable controversy regarding the potential role of zoonotic transmission, recent molecular studies allow the conclusion that most dog and livestock *G. lamblia* isolates are genetically different from human isolates, indicating that these organisms are not major sources of human infection. In contrast, cats and beavers harbor genotypes that are the same as the human isolates, leaving open the possibility that human infection can be acquired from these animals.

Excystation occurs in the proximal small intestine, yielding the disease-causing trophozoites that replicate in the small intestine. Trophozoites adhere to the intestinal wall by mechanical suction generated by the ventral disk. The mechanism of diarrhea is unknown, since invasion does not occur and no toxins have been identified. Many people remain asymptomatic, but those with symptoms have diarrhea with loose foul-smelling stools and bloating. Weight loss is common and symptoms frequently last weeks or months in the absence of treatment. In the United States, giardiasis causes approximately the same number of hospitalizations as shigellosis. The diagnosis is usually established by the identification of cysts or trophozoites in fecal specimens or by detection of *Giardia* antigens in fecal specimens, either by indirect fluorescent antibody (IFA) or by enzyme-linked immunosorbent assay. The diagnosis can sometimes be made using a string test in which patients swallow a capsule on a string. After several hours, the capsule is examined microscopically for the presence of *Giardia* trophozoites. In patients with persistent diarrhea and malabsorption who have negative fecal examinations, upper endoscopy with small intestinal biopsy can be used to look for evidence of giardiasis or other small intestinal disease.

*Cryptosporidium parvum* is an apicocomplexan organism that was recognized as an important cause of diarrhea after the advent of the AIDS epidemic. Human infection results when oocysts are ingested, typically from contaminated water. The infections may be acquired from other humans or from livestock. An outbreak involving an estimated 400,000 persons in Milwaukee, Wisconsin, in 1993 may have resulted from human or livestock contamination of the water. In immunocompetent individuals, diarrhea with loose stools typically lasts approximately 1 week. However, in patients with advanced HIV infection, profuse watery diarrhea may persist for months, leading to dehydration. In addition, *C. parvum* may rarely disseminate to the gallbladder, causing symptomatic biliary disease. The asexual replication of merozoites in an intracellular, but extracytoplasmic space in small intestinal endothelial cells results in the symptoms. The diagnosis of intestinal disease is established when the oocysts are identified in fecal samples, either by routine staining or by acid-fast or fluorescence antibody staining. *Candida* spp. can be confused with *C. parvum* oocysts on routine stains, but the acid-fast stain will easily distinguish the two, since *C. parvum* oocysts are acid-fast. The diagnosis can also be established by identifying the merozoites in small intestinal endothelial cells obtained by intestinal biopsy. There is no known effective therapy for cryptosporidiosis, so treatment is supportive.

*Cyclospora cayetanensis* is a recently identified cause of diarrheal illness in humans. It was initially thought to be a cyanobacteria-like organism or a blue green alga, but in 1993, was described as an apicocomplexan, which is closely related to the poultry pathogens, the *Eimeria* spp. Cyclosporiasis gained prominence in the United States when it was associated with outbreaks of diarrheal disease acquired from imported raspberries in the summer of 1996 and subsequent summers. Human infections are initiated when sporulated oocysts are ingested followed by replication in the small intestine. Diarrhea with loose stools begins an average of 1 week after exposure and may last several weeks in the absence of therapy. The diagnosis is established by identifying the oocysts in fecal specimens from

infected persons after routine preparation or after acid-fast staining or by the detection of autofluorescing oocysts. To date, no nonhuman reservoirs have been identified.

*Trypanosoma cruzi* is a zoonotic organism that infects a variety of mammals throughout much of South and Central America and is transmitted from one host to another by the bite of a Reduviid (kissing) bug. Humans are accidental hosts and not part of the usual life cycle of the organism. Epimastigotes replicate in the Reduviid bug, followed by differentiation into metacyclic trypomastigotes. The infection results when the metacyclic trypomastigotes from the insect feces gain access through a mucous membrane surface or through compromised skin. The bite of the insect is intensely pruritic and the scratching that occurs after the bite may allow the *Tr. cruzi* epimastigotes access. The organisms then invade host cells, where they differentiate into amastigotes, replicate, and then differentiate into trypomastigotes followed by cell rupture and invasion of the next cell.

An acute illness with fever, local inflammation, and sometimes cardiac or central nervous system (CNS) manifestations may result. Most of these cases resolve spontaneously. Subsequently, whether or not symptoms are present acutely, some patients go on to a prolonged asymptomatic parasitemia (indeterminate phase). Some of those patients go on to develop chronic Chagas' disease, sometimes known as mega-gastrointestinal disease. The most common cause of morbidity and mortality is cardiomyopathy with concomitant ventricular arrhythmias. The other major cause of morbidity is hypertrophy and dilation of the gastrointestinal tract, most commonly the colon or esophagus. Patients may thus present with severe constipation or megacolon or with severe dysphagia and regurgitation. When the diagnosis is suspected in someone with an appropriate exposure history and clinical syndrome, serologic testing will usually support the clinical diagnosis. Endogenous cases in the United States have been documented rarely in Texas, but cases have been acquired through organ transplants from infected individuals and may also occur by blood transfusion. Anti-parasitic treatment is sometimes effective in acute infections, but is ineffective in chronic infections. Therefore, treatment of chronic infection is supportive.

The microsporidia are currently classified with the protozoa, but their classification is uncertain and they may belong to the fungi. They are obligate intracellular organisms and became recognized as significant human pathogens after the advent of the AIDS epidemic. Many species from multiple genera have been associated with human infection. *Enterocytozoon bieneusi* is the most common microsporidial infection in AIDS patients and infects the small intestine, biliary tract, and liver. Patients have diarrhea and malabsorption, with the severity and duration of disease depending on the level of immunosuppression. The diagnosis can be established by the identification of organisms in intestinal biopsy samples, by electron microscopy, or by routine histochemical methods. Sometimes the organisms can be detected in biliary, intestinal, or fecal fluids. Other microsporidia cause primarily disseminated or corneal disease.

## HELMINTHS

The helminths that cause human infections are classified as nematodes (roundworms), cestodes (flatworms), and trematodes (flukes). The nematodes are frequently divided intestine and tissue-dwelling organisms.

*Ascaris lumbricoides* (roundworm) infection is initiated when the ova are ingested from an environmental source. When larvae hatch from the ova, they migrate through the lungs, sometimes resulting in cough and pulmonary infiltrates. Blood eosinophilia is common at this time. The larvae are then swallowed and return to the small intestine where they become adult worms. Most infections result in no gastrointestinal symptoms, but heavy infections can result in intestinal obstruction due to a mass of adult worms. Biliary tract invasion occurs rarely, resulting in acute abdominal pain and biliary obstruction. In roundworm infections with no overt symptoms, malabsorption is common, especially in developing areas.

Hookworm infections are established when larvae from the soil penetrate the skin and migrate through the lungs. They are then swallowed to make their way to the small intestine. The initial phase of the infection may result in pruritis at the site of larval penetration or pulmonary symptoms similar to those of roundworm infections. The majority of infections do not result in gastrointestinal symptoms, but abdominal pain, diarrhea, and malabsorption may be seen, especially with heavy infections. The most important clinical consequence of infection is iron deficiency anemia, which is proportional to the worm burden and is more severe with Old World hookworms (*Ancylostona duodenale*) than with New World hookworms (*Necaor americanus*).

*Trichuris trichiura* (whipworm) infections are initiated by the ingestion of ova, followed by hatching into larvae in the small intestine and migration of the larvae to the large intestine, where the adult worm lays eggs. Most infections are probably asymptomatic, but heavy

infections can result in iron deficiency anemia, dysentery, or rectal prolapse.

*Trichinella spiralis* infections (trichinosis) are established when meat that contains larvae from infected mammals (e.g., pigs, polar bears) is ingested. Cooking and prolonged freezing kill the larvae, so the risk is greatest from fresh raw meat. Mild gastrointestinal symptoms may ensue within a week after infection, but most patients remain asymptomatic at this stage. After approximately 2 to 6 weeks, larval migration results in fever, headache, periorbital or facial edema, conjunctivitis, and neurologic symptoms. The severity of illness generally correlates with the degree of the initial inoculum. Eosinophilia is pronounced. Death may occur from heart failure or CNS involvement. A suspected diagnosis may be supported by serologic testing and confirmed by the detection of larvae in muscle biopsy specimens. Treatment consists of corticosteroids in addition to anti-helminthic therapy.

*St. stercoralis* third-stage (L3) larvae in soil infect humans by direct penetration of intact skin. They pass through the lungs and mature in the intestine into parthogenetic adult worms, which lay eggs that hatch in the intestine to form L1 larvae. The L1 larvae may then complete their life cycle in the soil. However, as part of the autoinfective cycle, the larvae can mature to the L3 stage in the intestine and migrate to a location in the intestine or elsewhere. The number of larvae in the typical *Strongyloides* infection is small, but in immunocompromised hosts (especially those on high doses of corticosteroids for prolonged periods of time), large numbers of larvae are produced through the autoinfective cycle. These larvae may invade extraintestinal sites such as the lungs and CNS, carrying bacteria with them as they go. These bacteria are actually the major cause of morbidity and mortality in overwhelming strongyloidiasis.

Schistosomiasis refers to disease caused by several species of the genus, *Schistosoma*. The *Schistosoma* species that infect humans cause most of their disease when the adult worms lay eggs in the venous system for which they are tropic, causing scarring and venous obstruction. *Schistosoma hematobium* infects the bladder and its venous system, whereas the other *Schistosoma* species infect the gastrointestinal system and are tropic for parts of the mesenteric venous system. The most common cause of gastrointestinal and mesenteric infection is *Schistosoma mansoni*; the others have similar clinical manifestations, but vary in their geographic distributions. *Sc. mansoni* infection is initiated when cercariae released by the intermediate host snail, which resides in freshwater, penetrate the intact skin. Pruritis (swimmer's itch) may develop at the time of cercarial penetration, but is more commonly associated with schistosomes that do not infect humans; these latter schistosomes may be encountered in the United States. Approximately 1 to 2 months after a massive *Sc. mansoni* or *Schistosoma japonicum* infection, patients may develop a syndrome with acute fever with systemic and pulmonary symptoms, called Katayama fever. They have hepatosplenomegaly, lymphadenopathy, and eosinophilia. Most people recover spontaneously, but deaths may occur, especially with *Sc. japonicum*.

However, most of the morbidity associated with schistosome infections is due to the chronic scarring that results. The degree of scarring is generally proportional to the worm burden and egg output of the infecting organisms. The cercariae transform into schistosomulae, which first migrate to the liver and lungs and then to the inferior mesenteric plexus, where they mature into adults and lay their eggs. The scarring results in elevated splenic and portal pressures with splenomegaly and portal hypertension. The diagnosis can be established by the identification of *Sc. mansoni* eggs in fecal specimens or in rectal biopsies. In endemic areas, liver ultrasound is very effective in evaluating the extent of hepatic fibrosis resulting from the chronic infection. Screening is important in these areas, since anti-helminthic treatment may eliminate the organisms and prevent scarring, but does not reverse scarring that has already occurred.

*Clonorchis senensis* is a liver fluke found in eastern Asia that infects fish-eating mammals, whereas *Fasciola hepatica* is found in sheep-raising areas throughout the world. Human infections with these parasites may result in symptomatic biliary disease.

The human is the definitive host for *Taenia saginata*, the beef tapeworm, and cattle are the intermediate hosts. Human infections are generally asymptomatic, although mild abdominal pain or diarrhea may result. Infections may be diagnosed by finding the eggs or the proglottids in fecal specimens. When only the eggs are found, they cannot be distinguished morphologically from those of *Taenia solium*.

Humans are normally the definitive hosts for *Ta. solium*, the pork tapeworm. The human infection results when inadequately cooked meat containing cysticerci (the larval form) is ingested. The tapeworm then matures in the intestine and lays eggs, which are passed in the feces to be ingested by the porcine intermediate host. This form of infection is relatively inconsequential. However, humans may develop cysticercosis when they become an accidental intermediate host by ingesting eggs either from their own infection or from another source. The larvae then migrate to muscles or brain, where they eventually calcify. The inflammatory

response and calcifications of cysterci in the brain may result in seizures or other CNS manifestations. In endemic areas, cysticercosis is the most common cause of adult-onset seizures. Cysticercosis can be diagnosed by the classic clinical findings as well as by serologic testing. Patients may have simultaneous intestinal infection, so fecal specimens should be examined in patients with a new diagnosis of cysticercosis.

Canines are the definitive hosts of the *Echinococcus* species and the intermediate hosts vary with the species. *Echinococcus granulosus* causes hydatid disease and is the most common species to infect humans. Domestic dogs are the usual definitive hosts and sheep and other livestock animals are the normal intermediate hosts, so the organism is endemic in many grazing areas. In the United States, most cases are found in sheep-grazing areas of southern Utah and northern Arizona. Human infections are initiated when people ingest eggs from canine feces, becoming accidental intermediate hosts. The eggs hatch to form oncospheres, which migrate to their final destination to form larval cysts. The most common location is the liver, but the lungs or other organs may also be involved. Symptoms usually result from the space-occupying effect of the cysts, but an abrupt onset of fever with hypotension or even anaphylaxis can result from accidental rupture of a cyst. Imaging with ultrasound or CT scanning yields characteristic results and the suspected diagnosis can be confirmed by serologic testing. Therapy may consist of medical (albendazole) and/or surgical therapy and should be individualized. When needle aspiration or surgical excision of a possible echinococcal lesion is performed, care must be taken to avoid spilling the contents into the peritoneum, which could lead to life-threatening anaphylaxis or spreading of the infection. *Echinococcus multilocularis* causes a more aggressive disease (alveolar hydatid disease), since the cysts produce buds that metastasize throughout the body. Although liver lesions are the most common lesions, life-threatening cerebral lesions may also result. The usual definitive hosts of *Ec. multilocularis* are northern foxes and the intermediate hosts are the rodents on which the foxes feed; therefore, the organism is endemic to parts of the Arctic and sub-Arctic regions.

## See Also the Following Articles

**Amebiasis • Cestodes • Chagas' Disease • *Cryptosporidium* • Giardiasis • Helminth Infections • Nematodes • Trematodes • *Trichinella***

## Further Reading


Adam, R. D. (2001). Biology of *Giardia lamblia*. *Clin. Microbiol. Rev.* 14, 447–475.

Bhatia, G. (1997). Echinococcus. Semin. *Respir. Infect.* 12, 171–186.

Capo, V., and Despommier, D. D. (1996). Clinical aspects of infection with *Trichinella* spp. *Clin. Microbiol. Rev.* 9, 47–54.

Chen, X. M., Keithly, J. S., Paya, C. V., and LaRusso, N. F. (2002). Cryptosporidiosis. *N. Engl. J. Med.* 346, 1723–1731.

Clark, D. P. (1999). New insights into human cryptosporidiosis. *Clin. Microbiol. Rev.* 12, 554–563.

Didier, E. S. (1998). Microsporidiosis. *Clin. Infect. Dis.* 27, 1–7.

Espinosa-Cantellano, M., and Martinez-Palomo, A. (2000). Pathogenesis of intestinal amebiasis: From molecules to disease. *Clin. Microbiol. Rev.* 13, 318–331.

Franzen, C., and Muller, A. (1999). Molecular techniques for detection, species differentiation, and phylogenetic analysis of microsporidia *Clin. Microbiol. Rev.* 12, 243–285.

Herwaldt, B. L. (2000). *Cyclospora cayetanensis*: A review, focusing on the outbreaks of cyclosporiasis in the 1990s. *Clin. Infect. Dis.* 31, 1040–1057.

Katz, D. E., and Taylor, D. N. (2001). Parasitic infections of the gastrointestinal tract. *Gastroenterol. Clin. North Am.* 30, 797–815.

MacDonald, A. S., Araujo, M. I., and Pearce, E. J. (2000). Immunology of parasitic helminth infections. *Infect. Immunity* 70, 427–433.

Mandell, G. L., Bennett, J. E., and Dolin, R. (eds.) (2000). "Principles and Practice of Infectious Diseases." Churchill Livingstone, Philadelphia, PA.

Marshall, M. M., Naumovitz, D., Ortega, Y., and Sterling, C. R. (1997). Waterborne protozoan pathogens. *Clin. Microbiol. Rev.* 10, 67–85.

Nichols, G. L. (2000). Food-borne protozoa. *Br. Med. Bull.* 56, 209–235.

Ortega, Y. R., and Adam, R. D. (1997). *Giardia*: Overview and update. *Clin. Infect. Dis.* 25, 545–549.

Petri, W. A. Jr., and Singh, U. (1999). Diagnosis and management of amebiasis. *Clin. Infect. Dis.* 29, 1117–1125.

Ross, A. G., Bartley, P. B., Sleigh, A. C., Olds, G. R., Li, Y., Williams, G. M., and McManus, D. P. (2002). Schistosomiasis. *N. Engl J. Med.* 346, 1212–1220.

Siddiqui, A. A., and Berk, S. L. (2001). Diagnosis of *Strongyloides stercoralis* infection. *Clin. Infect. Dis.* 33, 1040–1047.

Umezawa, E. S., Stolf, A. M., Corbett, C. E., and Shikanai-Yasuda, M. A. (2001). Chagas' disease. *Lancet* 357, 797–799.

# Parasympathetic Innervation

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**dorsal vagal complex** The parasympathetic center in the brainstem (medulla oblongata) where sensory signals from the gut and motor outflow to the gut are integrated.

**efferent neuron** A neuron that transmits signals from the brain or spinal cord to the gut.

**Three divisions of the autonomic nervous system innervate the digestive tract. One is the parasympathetic division; the other two are the sympathetic and enteric divisions. The parasympathetic division is subdivided anatomically into the cranial and sacral divisions due to the neuroanatomic organization in which neurons that send fibers to the gut are located both in the brainstem and in the sacral region of the spinal cord. Projections to the digestive tract from these regions of the central nervous system are termed preganglionic efferents.**

## PARASYMPATHETIC NEURONS

Neuronal cell bodies of the parasympathetic cranial division reside in the medulla oblongata and project out of the brain in the vagus nerves (see Fig. 1). Cell bodies of the sacral division are located in the sacral region of the spinal cord and project in the pelvic nerves to the large intestine. Efferent fibers in the pelvic nerves make synaptic contact with neurons in ganglia located on the serosal surface of the colon and in ganglia of the enteric nervous system deeper within the large intestinal wall. Efferent vagal fibers form synaptic connections with neurons of the enteric nervous system in the esophagus, stomach, small intestine, and colon, as well as in the gallbladder and pancreas.

## DORSAL VAGAL COMPLEX

Cell bodies of efferent vagal neurons are in the dorsal motor nucleus of the medulla oblongata. They are part of the dorsal vagal complex, which consists of the dorsal motor nucleus of the vagus, nucleus tractus solitarius, area postrema, and nucleus ambiguous. The nucleus tractus solitarius handles the sensory information entering the brain from the gut. The area postrema is a chemical sensor that signals the presence of agents in the blood and the nucleus ambiguous consists of motor neurons, some of which project to innervate the esophagus.

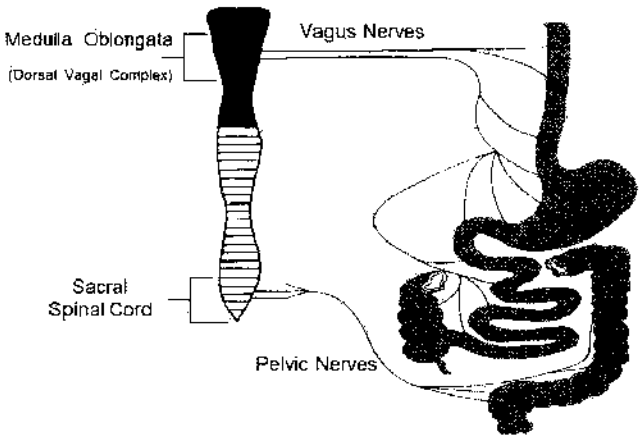


**FIGURE 1** The parasympathetic division of the autonomic nervous system has cranial and sacral divisions. The cranial division consists of nerve cell bodies located in the medulla oblongata and the projections of the vagus nerves to the digestive tract. Cell bodies of neurons of the sacral division are positioned in the sacral region of the spinal cord. They project from the pelvic nerves to the large intestine.

The dorsal vagal complex is the central integrative center for the outflow of signals from the brain to the gut. This center in the brain is more directly involved in the control of the specialized digestive functions of the esophagus, the stomach, and the functional cluster of the duodenum, gallbladder, and pancreas than in the distal small bowel and large intestine. The circuits in the dorsal vagal complex and their interactions with higher centers are responsible for the rapid and more precise control required for adjustments to rapidly changing conditions in the upper digestive tract during anticipation, ingestion, and digestion of meals of varied composition.

 

## FUNCTION

Efferent nerves of the cranial parasympathetic division transmit signals to the enteric innervation of the gastrointestinal musculature to control digestive processes both in anticipation of food intake and following the meal. This involves both stimulation and inhibition of contractile behavior in the stomach, stimulation of gastric acid secretion, stimulation of pancreatic secretion, and contraction of the gallbladder. Stimulation of inhibition or contraction results from activation of the enteric circuits that excite inhibitory or excitatory motor neurons, respectively.

Parasympathetic sacral efferents to the small and large intestinal musculature are predominantly stimulatory due to their input to the enteric microcircuits that control the activity of excitatory motor neurons. Signals transmitted by the sacral efferents are involved mainly in the initiation of defecation.

### See Also the Following Articles

Autonomic Innervation • Brain–Gut Axis • Defecation • Enteric Nervous System • Gastric Motility • Vagus Nerve

### Further Reading

Wood, J. (1999). "Neurogastroenterology and Motility." Milner-Fenwick, Timonium, MD.

Wood, J. (2003). Neurogastroenterology and digestive motility. *In* "Medical Physiology" (R. Rhoades and G. Tanner, eds.), 2nd Ed., Chap. 26, pp. 449–480. Lippincott Williams & Wilkins, Baltimore, MD.

# Parenteral Nutrition

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**enteral** Gastrointestinal feedings, either by mouth or through a tube placed in the stomach or intestinal tract.

**parenteral nutrition** The infusion of all essential nutrients by the intravenous route, bypassing the gastrointestinal tract. Also referred to as PN, total parenteral nutrition, artificial nutrition, intravenous feedings, or hyperalimentation.

**tonicity** A measure of the number of osmotic particles within a fluid. Isotonic refers to a similar number of particles in an intravenous solution and in the blood plasma. A hypertonic solution has a higher concentration of a solute than is found in blood.

**Parenteral nutrition is a method of feeding patients by infusing a mixture of all necessary nutrients into the circulatory system, thus bypassing the gastrointestinal tract. This approach is also referred to as intravenous nutrition, total parenteral nutrition, artificial nutrition, and hyperalimentation. This method of nutritional support is utilized in patients who cannot eat or take nutrients into the intestinal tract by tube feedings. In other situations, this method of feeding is indicated in patients who cannot absorb adequate nutrients due to gastrointestinal disease, injury, or loss of the intestinal tract and therefore can receive nutrients into the body only by intravenous infusion.**

## BACKGROUND

Intravenous fluids administered to hospitalized patients usually contain only sugar (glucose, also referred to as dextrose) and some minerals (usually only salt, sodium chloride). These solutions are similar in concentration (tonicity) to blood plasma and therefore this infusate does not injure the lining of the veins in the arms through which they are infused (this injury to veins is a process called phlebitis). Additionally, the isotonic solutions do not damage the circulating red blood cells. This means, however, that the

solutions can contain only 50 g of glucose per liter of solution. Because the usual adult patient requires only 2–3 liters of solution per day to maintain normal hydration, only 100–150 g of glucose will be delivered daily, providing approximately 400–600 cal/day. This amount of energy is inadequate to meet the daily energy requirements of the usual adult, which usually range from 1500 to 2500 kcal/day, and these needs may be further increased due to disease and weight loss.

The breakthrough in the development of parenteral nutrition came on two fronts. First, dietary fat (soybean oil) was emulsified and provided as lipid particles, which were safe and well tolerated when administered intravenously. Next, all other essential nutrients (glucose, amino acids, electrolytes, vitamins, and minerals) were mixed together to make a highly concentrated solution. This nutrient mix was combined with the fat emulsion and infused slowly into the superior vena cava (the large vein that drains blood from the head, upper chest, and arms into the heart) via a central venous infusion catheter. The concentrated solution was rapidly diluted by the high level of blood flow through the heart and the nutrients were delivered by the bloodstream to all organs of the body. Infusion of this concentrated solution into an arm vein causes severe chemical phlebitis, resulting in extensive local inflammation and clotting at the infusion site. Infusion through the central venous catheter, however, allowed adequate nutrients to be delivered in a reasonable volume of fluid without this complication occurring.

Approximately 35 years ago, researchers demonstrated the efficacy of this approach by feeding beagle puppies for up to 1 year entirely by the intravenous route. Normal growth and development were observed. Next, the mixture was infused into an infant who was born with only a short length of small intestine, inadequate to maintain sufficient absorption. The child was sustained by intravenous feedings for up to 2 years while surgical correction of the bowel was undertaken. During this time, the baby also demonstrated normal growth and development. These were the first demonstrations that by infusing all necessary nutrients by the intravenous route and bypassing the gastrointestinal tract of an organism normal growth and development could be achieved.

## INDICATIONS

In adults, the general indications for parenteral feedings include hospitalized patients who cannot take food or tube feeding formulas by the enteral route (e.g., via the intestinal tract). In well-nourished individuals, 7–10 days of conventional intravenous support (using 5% dextrose solutions) is generally provided, but if the period of partial starvation is to extend beyond this time, parenteral nutrition is indicated to prevent the potential complications associated with malnutrition. If the duration of illness is known to extend beyond 10 days, such as occurs in patients with severe pancreatitis, major trauma, or burn injuries, and enteral feedings are impossible, parenteral nutrition is initiated at an earlier stage in the hospital course. If the patient is malnourished as indicated by weight loss, the feedings will also be started as soon as the patient has stabilized. Preoperative patients with weight loss (greater than 15% normal body weight) who cannot take enteral feedings may also benefit from a course of parenteral nutrition for 7–10 days before surgery.

Individuals who have undergone massive intestinal resection may also require parenteral nutrition as a form of long-term nutritional support. Others with inflammatory bowel disease, severe malabsorption, and motility and obstructive disorders also frequently require such intravenous support.

Premature infants have minimal body stores of adipose and lean tissue and often require several weeks of intravenous feedings before full enteral feeding is possible. Therefore, parenteral nutrition is often utilized in these infants and those requiring surgical correction of major gastrointestinal anomalies.

## NUTRITIONAL REQUIREMENTS

In order to provide adequate nutrients to an individual patient, the specific nutritional requirements of the individual must be determined. These needs may differ from requirements that were present during health; malnutrition is associated with deficits that need repair and many diseases are associated with infection and inflammation that impose increased requirements for many nutrients.

### Energy

Basal energy requirements are a function of the individual's weight, age, gender, and activity level and the disease process. In general, hospitalized adults require approximately 25–30 kcal/kg/day but these requirements may be greater in patients with injury or infection (see Table I).

### Protein

Protein (or amino acids, the building blocks of proteins) is the functional and structural component of the

TABLE I Energy Requirements

| Patient condition | Basal metabolic rate | Approximate energy requirement (kcal/kg/day) |
|---|---|---|
| No postoperative complications, gastrointestinal fistula without infection | Normal | 25–30 |
| Mild peritonitis, long-bone fracture or mild to moderate injury | 25% above normal | 30–35 |
| Severe injury or infection | 50% above normal | 35–45 |
| Burn 40–100% of total body surface | Up to 100% above normal | 35–60 |

body. With disease, poor food intake, and inactivity, body protein is lost and individuals become weak and waste muscle mass. Protein requirements for most healthy individuals are 0.8 g/kg/day (approximately 40–70 g of protein/day). Critically ill patients may need 1.5–2.0 g protein/kg/day (approximately 60–150 g/day) depending on the disease process, but this amount is often reduced in patients with kidney or liver disease.

### Vitamins and Minerals

These requirements are usually met when standard volumes of a nutrient mix are provided. Increased amounts of vitamins are usually provided to severely ill patients (Table II) and blood levels are periodically determined to adjust the infusion levels of minerals such as sodium, potassium, chloride, phosphorous, magnesium, and zinc. Trace elements are usually added daily (Table III).

## APPLICATION

### The Solution

The patient is assessed and the nutritional requirements are determined by a physician, dietician, or other skilled provider. A prescription is submitted to the pharmacy or nutrition-mixing service for a mixture of parenteral nutrients to be composed for the specific patient. The nutrients are usually placed in 2- to 3-liter plastic bags and the contents are infused daily (Table IV). Alternatively, premixed solutions can be taken off the shelf and utilized but the fixed nutrient concentration limits the versatility of this approach in a heterogeneous patient population.

### The Central Venous Catheter

To administer the highly concentrated nutrient solutions, a catheter must be placed into the central venous system with its tip in the superior vena cava.

TABLE II Vitamin Requirements

| Vitamin | Units | Recommended dietary allowance (RDA) for daily oral intake | Daily requirement of the moderately injured | Daily amount provided by standard intervenous preparations |
|---|---|---|---|---|
| Vitamin A (retinol) | IU | 1760 (females)–3300 (males) | 5000 | 3300 |
| Vitamin D (ergocalciferol) | IU | 200 | 400 | 200 |
| Vitamin E (tocopherol) | mg | 8–10 | Unknown | 10 |
| Vitamin K (phylloquinone) | μg | 20–40 | 20 | 0 |
| Vitamin C (ascorbic acid) | mg | 60 | 75 | 100 |
| Thiamine (vitamin $B_1$) | mg | 1.0–1.5 | 2 | 3 |
| Riboflavin (vitamin $B_2$) | mg | 1.2–1.7 | 2 | 3.6 |
| Niacin | mg | 13–19 | 20 | 40 |
| Pyridoxine (vitamin $B_6$) | mg | 2.0–2.2 | 2 | 4 |
| Pantothenic acid | mg | 4–7 | 18 | 15 |
| Folic acid | mg | 0.4 | 1.5 | 0.4 |
| Vitamin $B_{12}$ | μg | 3.0 | 2 | 5 |
| Biotin | μg | 100–200 | Unknown | 60 |

TABLE III Trace Mineral Requirements

| Mineral | Recommended dietary allowance (RDA) for daily oral intake (mg) | Suggested daily intravenous intake (mg) |
|---|---|---|
| Zinc | 15 | 2.5–5.0 |
| Copper | 2–3 | 0.5–1.5 |
| Manganese | 2.5–5.0 | 0.15–0.8 |
| Chromium | 0.05–0.2 | 0.01–0.015 |
| Iron | 10 (males)–18 (females) | 3 |

Such a catheter can be placed via the subclavian vein, through a neck vein (the jugular vein approach is less desirable because of the high rate of associated infection), or by using a long catheter placed in an arm vein and then threaded into the central venous system (a peripherally inserted central catheter line) (Fig. 1). Once the correct position of the catheter has been established (usually by X ray), the infusion can begin.

### Administration

To ensure that the solution is administered at a continuous rate, an infusion pump is utilized to administer the solution. In hospitalized patients, infusion usually occurs over 22–24 h/day. In ambulatory home patients, administration usually occurs overnight (12–16 h).

### Monitoring

With solution infusion, a variety of determinations are made to ensure that the individual is responding appropriately to the infusate. This step involves primarily the measurement of glucose in the blood or urine (using techniques similar to those utilized by diabetic patients when monitoring sugar levels) but monitoring may be much more frequent and complex in critically ill patients. Urine output is measured over each 24 h period. In hospitalized patients, these measurements are usually performed by a highly trained nurse.

TABLE IV The Composition of a Standard Liter of Adult Parenteral Nutrient Solution

| | |
|---|---|
| Glucose | 150 g |
| Amino acids | 42 g |
| Sodium | 50 mEq |
| Chloride | 60 mEq |
| Potassium | 40 mEq |
| Phosphorous | 15 mg |
| Acetate | 75 mEq |
| Magnesium | 12 mEq |
| Sulfate | 12 mEq |
| Calcium | 5 mEq |
| Gluconate | 5 mEq |

### Variations Due to Age and Disease

Fluid volume and nutrient concentration must vary in pediatric patients depending on their age and weight. In adults with abnormal fluid loss, renal or liver failure, or other metabolic disorders, special mixtures are compounded to meet specialized fluid and nutrient requirements.

## PERIPHERAL VEIN NUTRITION

Slightly hypertonic nutrition solutions can be prepared from commercially available amino acid mixtures (5%) dextrose solutions (10%), and fat emulsions (20%). These nutrient mixtures have a low caloric density (approximately 0.3 to 0.6 kcal/ml) and thus provide only 1200 to 2300 kcal/day in 2000 to 3500 ml of solution. The advantage to using these dilute nutrient mixtures is that they can be infused through a plastic cannula placed in a large-bore arm vein, thus avoiding the central catheter. This approach may be useful in the short term or, combined with minimal feedings administered via the gastrointestinal tract, the two methods of nutrient administration together may provide adequate nutrient requirements to a critically ill patient. These solutions tend to cause phlebitis (inflammation) of the arm veins and the infusion site must be inspected frequently and the infusion site changed every 48–72 h. Thus, this approach is acceptable only as a short-term solution to delivery of the parenteral nutrients.

## COMPLICATIONS AND MONITORING

### Catheter Care and Catheter Sepsis

Although it is not the most common problem related to intravenous feedings, catheter infection is probably the most common, serious problem related to this technique. The catheter is a plastic or Silastic tube that passes through a skin puncture site and then enters

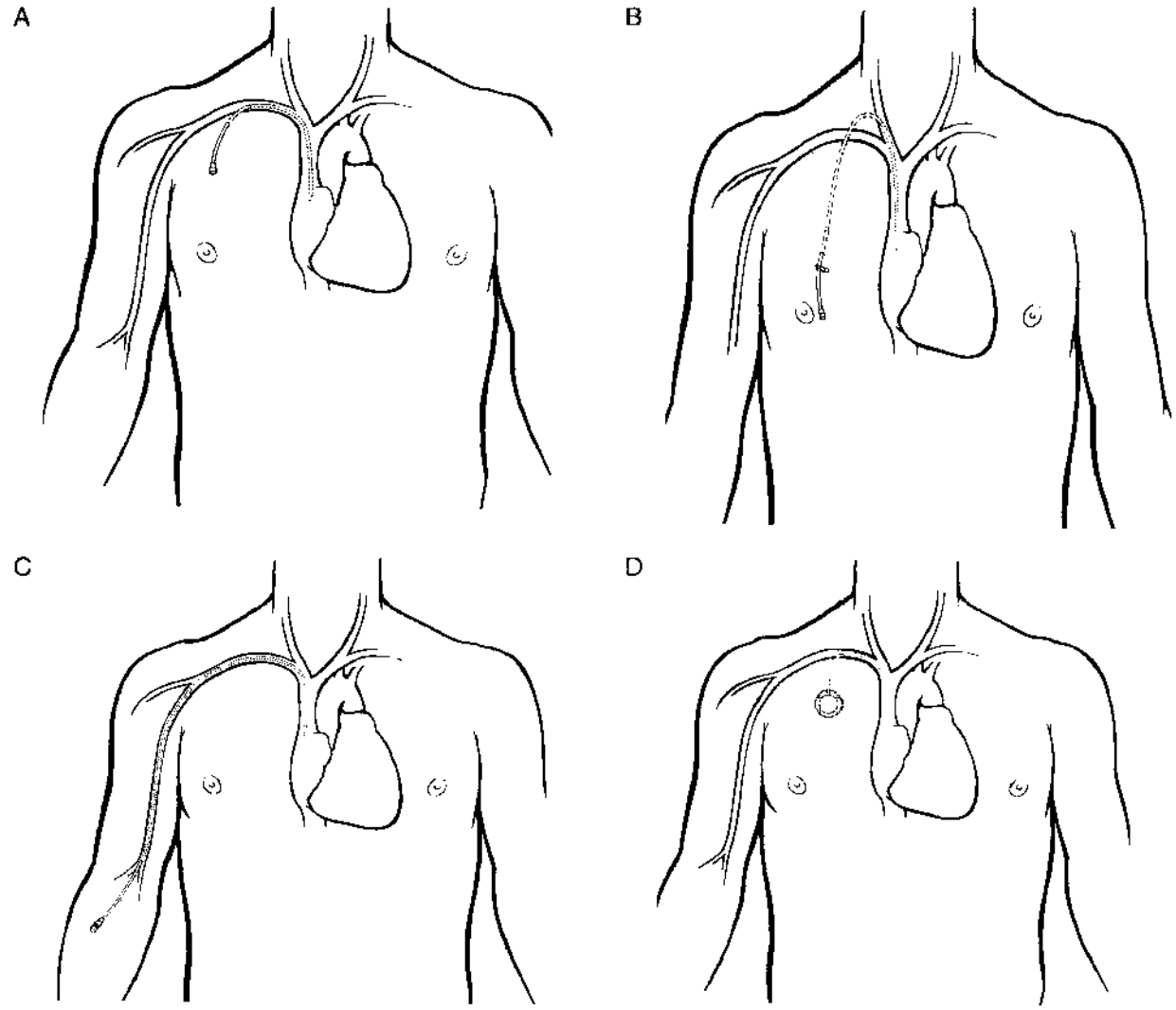


FIGURE 1 (A) This is a central venous catheter placed in the subclavian vein with its tip in the superior vena cava. (B) In the operating room, a catheter is inserted into the jugular vein in the neck and is directed into the superior vena cava. The distal portion of the catheter is tunneled under the skin to provide a subcutaneous tract that will resist infections. This device, which is inserted in patients requiring long-term (home) therapy, is often referred to as a Hickman catheter. (C) This fine plastic catheter is placed in an arm vein and is directed into the superior vena cava. This procedure is performed at the bedside, usually by a highly trained nurse. This approach is commonly referred to as a PICC (peripherally inserted central catheter) line. (D) This catheter is buried entirely below the skin and has a circular port covered by a rubber diaphragm, which is placed just below the skin. The patient intermittently pierces the skin and underlying diaphragm with the infusion needle in preparation for the nutrient infusion. The needle is removed at the termination of the therapy, so that no external catheter is visible.

the circulatory (venous) system. Thus, the catheter entrance site may serve as a portal for the entry of bacteria and other microorganisms into the body. In addition, many individuals requiring this therapy have inadequate mechanisms to fight infection, making these malnourished or critically ill patients all the more vulnerable to this completion of catheter sepsis (infection).

Catheter sepsis is characterized by the classic signs of infection: chills, fever, and, on occasion, drainage around the catheter entrance site. The white blood cell count is usually elevated and frequently

microorganisms are cultured from the bloodstream or the catheter tip. Fortunately, with removal of the infusion catheter, the symptoms usually abate in most patients. A short course of antibiotics is then usually adequate to clear the infection. However, many critically ill patients have fever from other sources (pneumonia or wound infections, for example) and the presence of this symptom complex associated with fever in a seriously ill patient often makes accurate diagnosis of catheter infection very difficult.

To prevent this complication, a rigorous program of catheter care is followed. Only intravenous nutrition solutions are administered through the catheter and no blood may be withdrawn from the catheter. Two to three times weekly, the dressing around the catheter is removed and, using sterile technique, the skin around the entrance site is scrubbed to reduce the number of microorganisms on the skin, thus decreasing the chance of catheter infection. The entrance site is inspected for signs of inflammation and drainage and if present, cultures are usually taken or the catheter is removed. Sterile technique is also utilized while attaching a new bag of nutrient solutions to the catheter for infusion. Catheter care and administration of the nutrient solution are generally carried out by a specially trained member of the nursing staff or a nurse with expertise in this field assigned to the nutritional support service.

## Metabolic Complications

Although there is wide potential for problems (Table V) because of the variability in the patient's clinical status, metabolic complications are generally minimized by the adherence to a strict monitoring protocol (Table VI).

The major concern is the occurrence of hyperglycemia (an elevated blood sugar), which is associated with the infusion of excess glucose in the feeding solution or the diabetic-like state in the patient associated with many critical illnesses. Hyperglycemia can result in an osmotic diuresis (abnormal loss of fluid via the kidney), dehydration, and hyperosmotic coma. A diagnosis is made by the presence of elevated blood glucose levels and the detection of sugar in the urine. When this complication occurs, the infusion solution may be reformulated to decrease the amount of infused

TABLE V Some Metabolic Complications of Parenteral Nutrition

| Problems | Possible causes | Solution |
|---|---|---|
| Glucose | | |
| Hyperglycemia, glycosuria, osmotic diuresis, hyperosmola nonketotic dehydration, and coma | Excess quantity of glucose infused; inadequate endogenous insulin; increased glucocorticoids; sepsis | Reduce quanity of glucose infused |
| Ketaocidosis in diabetes mellitus | Inadequate endogenous insulin response; inadequate exogenous insulin therapy | Administer exogenous insulin; reduce glucose |
| Fat | | |
| Altered coagulation | Hyperlipidemia | Decrease administration rate |
| Hypertriglyceridemia | Rapid infusion; decreased clearance | Decrease administration rate |
| Impaired liver function | May be caused by fat emulsion or by an underlying disease process | Consider infusions for only 16–18 h/day |
| Essential fatty acid deficiency | Inadequate essential fatty acid administration | Administer fat emulsion |
| Amino acids | | |
| Serum amino acid imbalance | Unphysiologic amino acid profile of the nutrient solution; ?? amino acid utilization with various disorders | Change type of amino acid mixture administered |
| Hyperammonemia | Excessive ammonia in protein hydrolysate solutions; deficiency of specific amino acids; primary hepatic disorder | |
| Prerenal asotemia | Excessive amino acid infusion with inadequate calorie administration; inadequate free water intake; dehydration | Reduce amino acid intake |
| Elevated or subnormal blood levels of electrolytes and minerals | Inadequate or excess administration | Adjust administration rate; evaluate underlying pathophysiology |

TABLE VI Monitoring Patients Receiving Parenteral Nutrition

| Variables | Suggested monitoring frequency | |
|---|---|---|
| | First week | Later |
| **Energy balance** | **Daily** | **Daily** |
| Weight | | |
| **Metabolic variables** | | |
| *Blood measurements* | Daily | 1–2 × weekly |
| Plasma electrolytes ($Na^+$, $K^+$, $Cl^-$) | 3 × weekly | 2 × weekly |
| Blood urea nitrogen | 3 × weekly | 2 × weekly |
| Plasma total calcium and inorganic phosphorus | Daily | 3 × weekly |
| Blood glucose | 3 × weekly | 2 × weekly |
| Plasma transaminases | 2 × weekly | Weekly |
| Plasma total protein and fractions | As indicated | As indicated |
| Blood acid–base status | Weekly | Weekly |
| Hemoglobin | 2 × weekly | Weekly |
| Magnesium | Weekly | Weekly |
| Triglycerides | | |
| *Urine measurements* | Daily | Daily |
| Glucose | Daily | Daily |
| Specific gravity or osmolarity | | |
| *General measurements* | Daily | Daily |
| Volume of infusate | Daily | Daily |
| Oral intake (if any) | Daily | Daily |
| Urinary output | | |
| **Prevention and detection of infection** | | |
| Clinical observations (activity, temperature, symptoms) | Daily | Daily |
| WBC and differential counts | As indicated | As indicated |
| Cultures | As indicated | As indicated |

glucose (usually the glucose infused should not exceed 4 mg/kg/min). Alternatively, insulin can be administered (either administered by subcutaneous injection or placed in the infusion bag).

The patient may also accumulate triglycerides in the bloodstream with infusion of the fat emulsion. Infusion of both glucose and fat emulsion in excess may result in pulmonary insufficiency. With excess glucose infusion, excess carbon dioxide ($CO_2$) production occurs as $CO_2$ accumulates in the bloodstream, a result of glucose metabolism. With lipid infusion, the lipid particles may accumulate in the lungs and reduce the diffusion capacity of respiratory gases.

In addition to these metabolic problems, the concentrations of a variety of electrolytes and minerals may vary and these levels are monitored by frequently determining concentrations in the bloodstream. Adjustments in the concentrations of the nutrients in the infusates are then made.

### Mechanical Complications

As with any device, catheters and tubing may become clotted or twist and obstruct. Pumps may also fail or operate improperly. Of more concern is the infrequent complication of superior vena cava thrombosis, which is related to the catheter being placed in this large vein. This complication is associated with clotting of this large vessel draining the upper body and results in swelling of the arms and face. This occurs more commonly in children than adults but usually prevents further intravenous support and thus poses a serious life-threatening problem to many patients when this complication occurs.

## HOME PARENTERAL NUTRITION

Patients who are unable to eat and absorb adequate nutrients for maintenance over the long term may be candidates for home parenteral nutrition. Many such individuals suffer from short-bowel syndrome caused by loss of the intestinal tract due to (1) extensive Crohn's disease, (2) mesenteric infarction, or (3) severe abdominal trauma. Pseudo-obstruction, radiation eneteritis, carcinomatosis, necrotizing enterocolitis, and intestinal fistulas are other reasons for poor bowel function and indications for home nutritional support.

To be eligible for this home parenteral nutritional therapy, patients must be able to master the techniques associated with this support system, be motivated, and have adequate social support in the home. Patients receive extensive evaluation, teaching, and training during a period of hospitalization that covers basic principles of parenteral nutrition and provides guidelines for catheter care, the maintenance of asepsis, and the use of infusion pumps.

A patient who is judged to be a candidate for home parenteral nutrition requires an indwelling Silastic catheter designed for long-term permanent use (see Fig. 1).

The nutrient solutions are prepared weekly and delivered to the patient's home. The patient sets up the infusion system and attaches the catheter to the delivery tubing in the evening for infusion over the next 12–16 h. The intravenous nutrition is terminated by the patient the next morning. Home care nurses see the patient at regular intervals and monitor infusion techniques, evaluate the patient's response to therapy, and continue the educational process for both the patient and family.

Home nutrition evolved because patients required this type of nutritional support for months or years, but costs of hospitalization made such therapy impossible in the hospital setting. This resulted in the development of private home care companies who have a support staff (including home nurses), mix and provide the solutions, maintain an inventory of supplies, respond to emergencies, and facilitate billing and collection for these services from insurers.

## EFFICACY

Though the need for nutrition support in critically ill patients may seem obvious, this method of care has only recently became subject to critical review and to the objective assessment of outcome and cost benefit. A summary of these findings follows.

In one report, a total of 13 prospective randomized trials that evaluated the use of preoperative parenteral nutrition in surgical patients were identified. The patients were considered by their physicians to be moderately malnourished. A pooled analysis of the data showed that patients who received preoperative TPN had 10% fewer postoperative complications than the control group. The analysis found no significant difference in mortality between the parenterally fed groups and the controls.

Use of parenteral nutrition in the immediate postoperative period was also evaluated. In contrast to the analysis of the preoperative data, this study of postoperative feeding concluded that patients who received TPN after an operation had an approximately 10% higher risk of ensuing complications, with no associated benefit.

Trials addressing perioperative nutritional support have also been conducted in patients undergoing surgery in the upper abdomen for gastroenterological malignancies. In one such study, patients undergoing major pancreatic resection were randomly assigned either to a group that received TPN on postoperative day 1 or to a non-TPN group. No significant benefit from the use of adjuvant TPN could be demonstrated and the incidence of complications (primarily those associated with infection) was significantly greater in the TPN group.

Finally, a large meta-analysis evaluated the effects of providing parenteral nutrition versus no feeding in 2211 critically ill patients. The use of intravenous feedings did not influence mortality but may have reduced the complication rate, especially in malnourished patients. The authors concluded that further studies were necessary to firmly establish the latter conclusion.

All of these studies indicate the need to identify specific targeted patient groups who will benefit from this complex and expensive technique. Broad-scale use of this nutritional support technique is not indicated.

## THE FUTURE

Because of costs, complications, and the ability to provide nutritional support by enteral tube feedings, the use of parenteral nutrition is decreasing in the United States. However, in specific patient groups it remains cost-effective and life-saving.

Several new components or products have become available to improve the type of substrate administered. New fat emulsions that include omega-3 fatty acids (fish oil) have been developed and these compounds are believed to be able to enhance the immune system in critically ill patients. In addition, some amino acids have not been included in the parenteral mixtures because of solubility problems or instability related to sterilization or prolonged shelf-life. However, these compounds have recently been combined with other amino acids to form stable dipeptides, which are now being included in the parenteral amino acid solutions. One such substance that is now available is the amino acid glutamine, which is thought to enhance immunological and bowel function in selected populations. This may translate into a method of nutritional support that improves recovery following major surgery and chemotherapy and improves resistance to infection in individuals with other life-threatening illnesses.

## See Also the Following Articles

Enteral Nutrition • Nutritional Assessment • Short Bowel Syndrome

## Further Reading

Baker, R. D., Jr., Baker, S. S., and David, A. M. (eds.) (1997). "Pediatric Parenteral Nutrition." Chapman and Hill, New York.

Dudrick, S. J., Wilmore, D. W., Vars, H. M., and Rhoads, J. E. (1968). Long-term total parenteral nutrition with growth, development, and positive nitrogen balance. *Surgery* 64, 134–143.

Klein, S., Kinney, J., Jeejeebhoy, K., *et al.* (1997). Nutritional support in clinical practice: Review of published data and recommendations for further research directions. *J. Parenteral Enteral Nutr.* 21, 133–156.

Rombeau, J. L., and Rolandelli, R. H. (eds.) (2000). "Clinical Nutrition: Parenteral Nutrition." W. B. Saunders, Philadelphia, PA.

Wilmore, D. W., and Dudrick, S. J. (1968). Growth and development of an infant receiving all nutrients exclusively by vein. *J. Am. Med. Assoc.* 203, 860–864.

# Parietal Cells

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cotransporter An ion transporter that carries more than one ion in the same direction across the outer cell membrane.

endocytosis The process by which a cell membrane folds inward to internalize substances.

exchanger An ion transporter that transports ions in opposite directions across the cell membrane.

exocytosis The release of substances in a vesicle by a process in which the membrane surrounding the vesicle fuses with the membrane surrounding the outside of the cell.

$H^+$,$K^+$-ATPase The hydrogen, potassium ATPase protein that pumps protons across the cell membrane in a 1:1 exchange for potassium ions.

microvilli Microscopic, hair-shaped cellular projections that contain F-actin in their cores.

secretagogue A substance, such as a hormone or paracrine signal, that stimulates secretion.

**Parietal cells are located within glands in the gastric mucosa. They have the unique ability to secrete a massive amount of hydrochloric acid (HCl), which sustains the highly acidic environment within the lumen of the stomach. The unusual morphology of the parietal cell has fascinated researchers for over 100 years. When parietal cells are stimulated by the appropriate secretagogues, they also undergo spectacular morphological transformations that are correlated with the activation of the enzyme $H^+$,$K^+$-ATPase. HCl is generated by the $H^+$,$K^+$-ATPase, acting in concert with ion channels and other ion transporters. The $H^+$,$K^+$-ATPase is composed of a catalytically active α-subunit and a β-subunit that targets the enzyme to the appropriate membrane compartment. The three major secretagogues, histamine, acetylcholine, and gastrin, stimulate HCl secretion by activating different signaling pathways that interact at the level of the parietal cell. Because of the common occurrence of peptic ulcer disease, the acid secretory function of the parietal cell has been studied extensively. However, the parietal cell has other functions. In human, monkey, cat, dog, sheep, rabbit, and guinea pig, parietal cells secrete intrinsic factor, which is essential for the efficient absorption of vitamin B12 or cyanocobalamin in the distal ileum. Parietal cells may also secrete prostaglandins as well as growth factors including transforming growth factor-α, amphiregulin, and heparin-binding epidermal growth factor. Prostaglandins exert a cytoprotective effect on the gastric mucosa and the local release of growth factors appears to play an important role in regulating the growth and differentiation of epithelial cells within the gland units.**

## LOCATION AND STRUCTURE OF THE PARIETAL CELL

Parietal cells are present in glands within the fundus and body of the stomach and are the largest cells in these

glands. They originate from immature progenitor cells in the gland isthmus and then migrate upward toward the pit region and downward toward the base of the gland. Parietal cells near the base of glands are smaller and frequently have dense accumulations of F-actin within their intracellular canaliculi. In contrast, parietal cells in the upper region of the gland have a more rounded appearance and contain more well-defined intracellular canaliculi. The designation "parietal" arose from the location of this cell within the gastric gland (bulging out along the wall; parietal being defined as relating to the walls of any hollow part of a plant or animal). Parietal cells are also referred to as oxyntic cells, based on the Greek word *oxyntos* (to generate an acidic substance). The "typical" parietal cell is usually depicted in a triangular shape with the apical region of the cell forming the apex of the triangle, which borders the lumen of the gastric gland. In stimulated parietal cells, the canaliculi are stylistically represented as simple bifurcations of microvillar membrane that extend partway into the cell. In reality, however, the intracellular canaliculi are complex, interconnected tubular systems that extend from the lumenally facing side of the cell to the basolateral membrane region (Fig. 1). The extensive array of intracellular membranes immediately beneath the intracellular canaliculi has historically been referred to as "tubulovesicles." This term was a compromise, because it was not possible to determine whether the membrane-rich structures detected with standard electron microscopy (EM) techniques were elongated tubules or round vesicles. Recent work, based on rapid freeze fixation and scanning EM as well as 3D reconstructions of transmission EM-based serial thin sections, suggests that the tubulovesicular system contains tightly packed cisternae that bear some resemblance to classical Golgi stacks.

FIGURE 1 The complexity of the intracellular canaliculus is not conveyed in simple drawings. (Left) Typical depiction of an actively secreting parietal cell with a simple canaliculus containing elongated microvilli (arrow). (Right) 3D reconstruction of confocal microscopic images of a parietal cell within a gastric gland. The gland was fixed and stained with fluorescently tagged phalloidin, which specifically labels F-actin. Reprinted from Chew, C. S., Parente, J. A., Jr., Chen, X., and Chaponnier, C. (2000). The LIM and SH3 domain-containing protein, lasp-1, may link the cAMP signaling pathway with dynamic membrane restructuring activities in ion transporting epithelia. *J. Cell Sci.* 113, 2035–2045. with permission.

## MORPHOLOGICAL CHANGES AND ION TRANSPORT ACTIVITIES ASSOCIATED WITH HYDROCHLORIC ACID SECRETION

In addition to complex internal membrane structures, parietal cells are unusually rich in F-actin and possess a large number of energy-generating mitochondria. When parietal cells are stimulated to secrete hydrochloric acid (HCl), the canalicular membrane compartment expands at the expense of the intracellular tubulocisternal membrane compartment and this expansion is correlated with the appearance of numerous elongated microvilli. The mechanism driving these changes is controversial. One view is that the two compartments are continuous. The other, which forms the basis of the membrane recruitment hypothesis originally proposed by John Forte and colleagues in 1977, is that the canalicular and tubulocisternal membranes are distinct intracellular compartments. The membrane recruitment hypothesis proposes that the activation of the acid secretory response induces an exocytotic-like insertion of tubulocisternal membrane containing the $H^+$,$K^+$-ATPase into the canalicular membrane. Removal of the stimulus results in an endocytotic retrieval of membrane plus the $H^+$,$K^+$-ATPase back into the tubulocisternal compartment. Currently, this latter hypothesis is favored and is supported by the localization of a number of proteins associated with vesicle recycling within the parietal cell, as well as by observations that the $H^+$,$K^+$-ATPase translocates to a biochemically distinct compartment following stimulation.

Parietal cell proteins associated with vesicular trafficking include SNAP-25 (25 kDa synaptosomal-associated protein), syntaxin 3, and VAMP-2 (vesicle-associated membrane 2), which form a ternary complex that is implicated in the docking and fusion of vesicles. Proteins associated with endocytosis that have been localized in the parietal cell include clathrin, clathrin adapters, and dynamin-2. Also present are SNAREs, which are also implicated in vesicle fusion; SCAMPs, which are transmembrane proteins found in vesicles involved in membrane recycling; myosin 5b; and several rab proteins including rab11a, rab11b, and rab25. Evidence from other cellular systems suggests a role for rab proteins in regulating vesicular trafficking

between membrane compartments. The expression of a dominant negative form of rab11a in gastric parietal cells also inhibits the recruitment of the $H^+,K^+$-ATPase to the canalicular membrane.

Although the relationship between changes in F-actin polymerization and microvillar elongation has not yet been established, changes in the plasticity of the actin cytoskeleton are implicated in this process. At least two different actin-binding proteins, ezrin and lasp-1, are highly expressed in the parietal cell and are regulated by the cyclic AMP (cAMP) signaling pathway. Parietal cells also contain two different pools of actin: γ-actin, which is present at the cortical cell membrane, and β-actin, which is present mainly within the canalicular region.

The precise biochemical steps associated with the generation of HCl are unknown. Protons are thought to be derived from $H_2O$ by the reaction, $HOH \rightarrow H^+ + OH^-$. Once generated, protons are actively extruded into the apically directed intracellular canaliculus by the $H^+,K^+$-ATPase in a neutral exchange for $K^+$. The activity of the $H^+,K^+$-ATPase is balanced by (1) the movement of $Cl^-$ through a $Cl^-$ channel and (2) the reuptake, or recycling, of $K^+$ through a $K^+$ channel. Although there are currently several candidates, the identity of these channels remains to be determined. The hydroxyl ($OH^-$) ions produced during the generation of protons combine with $CO_2$ in a reaction catalyzed by carbonic anhydrase to form bicarbonate ($HCO_3^-$), which is extruded from the cell by the action of $Cl^-/HCO_3^-$ exchangers (AE2 isoforms) on the basolateral membrane. When this bicarbonate enters the general circulation, the pH of the venous blood exiting the stomach rises above that of the arterial blood entering the stomach, a phenomenon that has been labeled the "alkaline tide."

In addition to $Cl^-/HCO_3^-$ exchangers, a $Na^+/K^+/2Cl^-$ cotransporter (NKCC1) resides on the basolateral membrane. Recent evidence suggests that there is a reciprocal relationship between the expression of the $Na^+/K^+/2Cl^-$ cotransporter and AE2. In rats, parietal cells above the neck of the glands express AE2 at high levels, whereas NKCC1 expression is not detectable. This distribution is reversed in the neck and the base of the glands. The differences in the distribution of these transporters suggest that there are at least two different populations of parietal cells with different $Cl^-$ entry mechanisms.

$Na^+/H^+$ exchangers (NHE2 isoforms) are also present on the basolateral membrane of the parietal cell. Although not directly coupled with AE2, these exchangers may act in concert with this $Cl^-/HCO_3^-$ exchanger in a pH-dependent manner, thereby indirectly mediating the transport of NaCl into the cell. The activities of NHE2 and AE2, coupled with the basolateral $Na^+,K^+$-ATPase, or sodium pump, and a basolateral $K^+$ conductance, may facilitate the uptake of $Cl^-$ into the cell against its electrochemical gradient. Based on targeted gene disruption studies, however, it appears that neither NHE2 nor NKCC1 is required for the acute acid secretory response.

## SIGNALING PATHWAYS INVOLVED IN THE REGULATION OF HYDROCHLORIC ACID SECRETION

Parietal cells possess receptors for histamine (H2-receptor subtype), acetylcholine (muscarinic M3 receptor subtype), and gastrin [cholecystokinin B (CCK-B) or $CCK_2$ receptor subtype] (Fig. 2). When histamine binds to H2 receptors, the enzyme adenylyl cyclase is activated through a stimulatory heterotrimeric G-protein, $G_s$, catalyzing the generation of cAMP from ATP. Once elevated, cAMP activates a cAMP-dependent protein kinase(s) that phosphorylates two F-actin-associated proteins, ezrin and lasp-1. The functions of these proteins in the activation of the acid secretory response have not yet been defined; however, their localization within F-actin-rich compartments supports a role in the regulation of changes in the actin cytoskeleton that accompany active secretion. The response to acetylcholine and gastrin involves the elevation of intracellular calcium concentrations ($[Ca^{2+}]_i$), presumably by coupling of the receptors with another heterotrimeric G-protein, $G_q$, which activates phospholipase Cβ. Once activated, this phospholipase catalyzes the breakdown of phosphatidylinositol 4,5-bisphosphate to form diacylglycerol (DAG), which activates protein kinase C, and inositol 1,4,5-trisphosphate ($IP_3$). $IP_3$ activates an intracellular calcium channel, the $IP_3$ receptor, allowing or calcium release from intracellular stores. Intracellular calcium release is coordinated with the influx of extracellular calcium through unidentified storage-operated calcium channels in the plasma membrane (Fig. 2). In isolated parietal cells, histamine weakly elevates $[Ca^{2+}]_i$ in a subpopulation of parietal cells, but this response is not coupled to the activation of HCl secretion. In contrast, the presence of extracellular calcium has been shown to be essential for cholinergic activation of secretion.

Although the intracellular signaling pathways that are activated by acetylcholine and gastrin are similar with respect to calcium, only acetylcholine elicits a significant acid secretory response in the absence of a histamine background. The reason for the divergence in

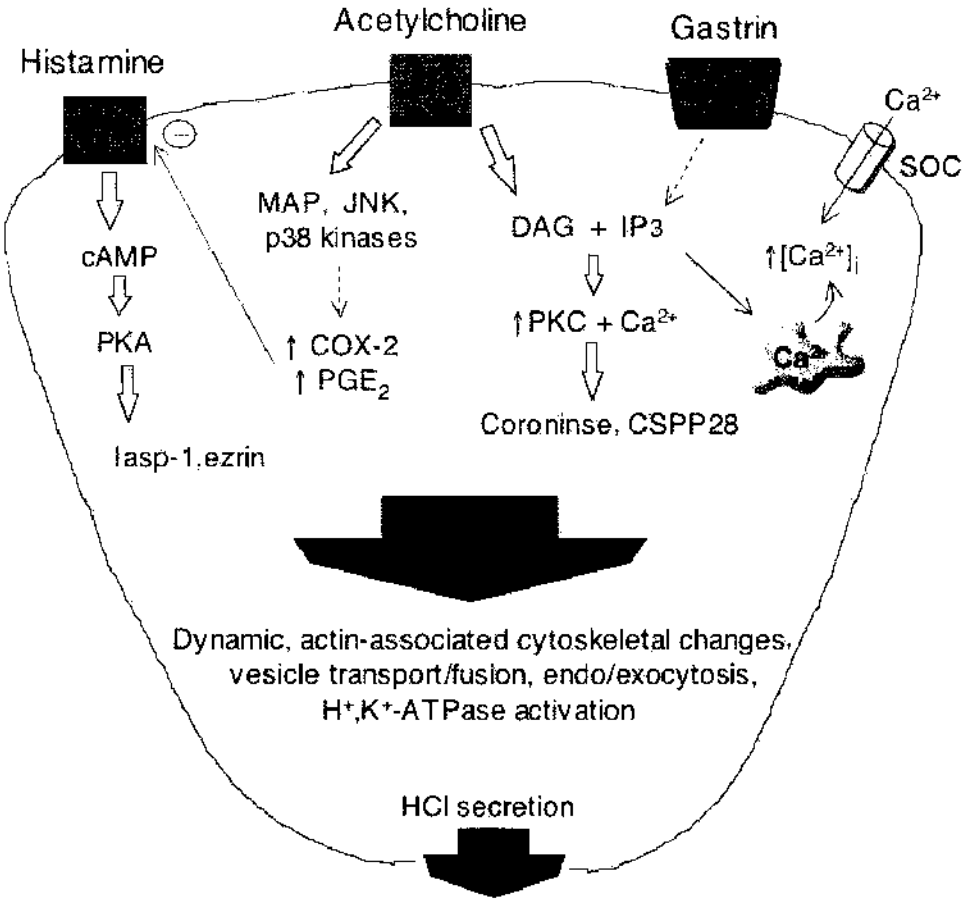


**FIGURE 2** Overview of the intracellular signaling pathways involved in the activation of parietal cell HCl secretion. When histamine binds to H2-type receptors, the enzyme adenylyl cyclase is activated and catalyzes the breakdown of ATP to form cAMP, leading to the activation of a cAMP-dependent protein kinase(s). These kinases phosphorylate lasp-1 and ezrin, which are F-actin-associated proteins. Acetylcholine and gastrin activate a calcium-dependent signaling pathway(s) by binding to muscarinic M3 and CCK2 receptors, respectively. Gastrin is a weak agonist at the level of the parietal cell and little is known about its actions beyond elevation of $[Ca^{2+}]_i$. It is also unknown how elevated cAMP levels potentiate the responses to acetylcholine and gastrin. Acetylcholine and gastrin induce the formation of $IP_3$ and DAG, presumably by activating phospholipase Cβ. $IP_3$ induces the release of $[Ca^{2+}]_i$ from intracellular stores. Calcium also enters the cell through an unidentified storage-operated calcium channel(s) (SOC) in the plasma membrane. Protein kinase C (PKC) and calcium-dependent protein kinase(s) are subsequently activated, leading to increases in phosphorylation of coroninse and CSPP28. Acetylcholine also activates ERK/JNK/p38 kinases and may increase the production of PGE2. This latter response could serve as a delayed autocrine negative feedback loop to regulate histamine-stimulated HCl secretion. The link between changes in protein phosphorylation and agonist-induced changes in the actin-based cytoskeletal has not yet been defined. However, recent evidence suggests that protein phosphorylation may be involved in regulating dynamic cytoskeletal changes and vesicle transport events involved in the insertion and retrieval of the $H^+,K^+$-ATPase from the canalicular membrane. Dashed lines indicate less established pathways.

the secretory response to acetylcholine and gastrin is unclear, but may be associated with differences in their signaling response patterns. Acetylcholine induces a greater rise in $[Ca^{2+}]_i$ than does gastrin. In addition, acetylcholine elicits a uniform response from parietal cells in isolation, whereas gastrin stimulates only ~30% of the same cells. Moreover, although both agonists appear to activate protein kinase C, they do not appear to increase the phosphorylation of the same downstream proteins. Acetylcholine also activates the mitogen-activated protein kinases [extracellular signal-related kinase variants 1 and 2 (ERKs 1 and 2)], JUN

N-terminal kinase (JNK), and possibly the p38 kinase signaling pathway. Recent evidence suggests that the activation of these latter pathways increases cyclooxygenase 2 (COX-2) gene expression and prostaglandin E2 (PGE2) production by the parietal cell. Increased PGE2 production may serve as a delayed negative feedback control pathway to regulate histamine-stimulated HCl secretion (see below).

As with histamine, the intracellular signaling events that that are modulated by cholinergic stimulation have just begun to be defined. Thus far, two proteins have been found to undergo increased phosphoryation in parietal cells stimulated with acetylcholine: coroninse and CSPP28. Coroninse is an actin-binding protein that has been implicated in the regulation of endocytosis. CSPP28 is phosphorylated by a calcium-dependent mechanism and is enriched in light membrane fractions. Thus, like coroninse, CSPP28 may be involved in controlling vesicle movement and/or fusion.

In most, but probably not all species, histamine and cAMP are the most powerful stimulators of the acid secretory response at the level of the parietal cell. There is an acute potentiating interaction between the cAMP and calcium signaling pathways such that a low dose of acetylcholine administered along with a submaximal dose of histamine induces a greater than additive response. There is a similar potentiating interaction between histamine and gastrin. The mechanisms responsible for these potentiating interactions are not yet established.

Several factors have been found to suppress the acute acid secretory response to histamine in isolated parietal cells, including prostaglandins of the E series, somatostatin, epidermal growth factor (EGF), and transforming growth factor-α (TGF-α). All of these factors appear to couple with an inhibitory heterotrimeric G-protein, $G_i$. Longer exposure of parietal cells in primary culture to EGF/TGFα enhances the acid secretory response. This long-term response may be initiated by activation of the serine/threonine protein kinase, Akt, and the induction of $H^+$,$K^+$-ATPase gene expression.

## See Also the Following Articles

**Exocytosis • Gastric Acid Secretion • Gastric $H^+$,$K^+$-ATPase • Gastrin • Histamine**

## Further Reading

Forte, J. G., and Yao, X. (1996). The membrane-recruitment and -recycling hypothesis of gastric HCl secretion. *Trends Cell Biol.* 6, 45–48.

McDaniel, N., and Lytle, C. (1999). Parietal cells express high levels of Na-K-2Cl cotransporter on migrating into the gastric gland neck. *Am. J. Physiol.* 276, G1273–G1278.

Okamoto, C. T., and Forte, J. G. (2001). Vesicular trafficking machinery, the actin cytoskeleton, and $H^+$,$K^+$-ATPase recycling in the gastric parietal cell. *J. Physiol.* 532, 287–296.

Schultheis, P. J., Clarke, L. L., Meneton, P., Harline, M., Boivin, G. P., Stemmermann, G., Duffy, J. J., Doetschman, T., Miller, M. L., and Shull, G. E. (1998). Targeted disruption of the murine $Na^+/H^+$ exchanger isoform 2 gene causes reduced viability of gastric parietal cells and loss of net acid secretion. *J. Clin. Invest.* 101, 1243–1253.

Soll, A. H., and Berglindh, T. (1994). Receptors that regulate gastric acid secretory function. *In* "Physiology of the Gastrointestinal Tract" (L.R. Johnson, ed.), 3rd Ed., Vol. 2, 1139–1169. Raven Press, New York.

# Pathologic and Paralytic Ileus

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**ileus** Absence of propulsive motility in the gastrointestinal tract.
**laparotomy** Surgical incision through the abdominal wall.
**physiologic ileus** Normal absence of gastrointestinal contractile activity.

**The term "ileus" is derived from the Greek word *eileos*, which is translated as "to block or to twist." Ileus is generally defined as absence of propulsive motility in the small or large intestine. Absence of propulsive motility implies stasis of the luminal contents. The presence of ileus can reflect normal intestinal physiology or it can be pathologic.**

## INTRODUCTION

Physiologic ileus refers to the absence of motility that normally occurs for short periods of time during specialized motility patterns, such as the inactivity found during the interdigestive state in the small intestine. Pathologic ileus refers to the prolonged absence of propulsive motility that is associated with clinical symptoms of an intestinal obstruction. Various names have been applied to this form of obstruction. It may be known as adynamic ileus, inhibitory ileus, or paralytic ileus. The latter term is not strictly accurate in a pathophysiologic sense because the intestinal musculature is not paralyzed in the same sense as in skeletal muscle paralysis.

## CLINICAL SYMPTOMS

Pathologic ileus can result from a variety of diverse conditions that include disease changes in the intestine and disease activity in the peritoneal cavity. Pathologic ileus may also be induced as a neurally mediated reflex response to conditions outside the peritoneum and may be associated with conditions such as general infections, spinal cord injury, and irritation of the kidneys. This form of obstructive intestinal inactivity is most commonly seen during and for prolonged periods following laparotomy. Exposure and handing of the bowel is a strong stimulus for the production of ileus. Nevertheless, the most clinically important cause of pathologic ileus is peritonitis.

The entire intestine in pathologic ileus becomes dilated with large collections of both fluid and gas. The gaseous composition is mostly air. Unlike mechanical obstruction whereby the intestine above the point of occlusion becomes distended gradually, dilatation of the entire bowel occurs quickly, with thinning of the wall as the radius increases. This underlies the extreme degree of abdominal distension that is one of the primary signs of the condition.

The clinical features of pathologic ileus do not parallel those found in mechanical obstruction. Pain is usually not a complaint, or, if present, is a dull continuous ache rather than the intermittent sharp cramping pain that occurs in structural blockage. Nausea and vomiting can be prominent and fluids given by mouth are regurgitated. Defecation and the passage of gas usually stop completely with the onset of the ileus.

## PATHOPHYSIOLOGY

Paralytic ileus is not entirely applicable as a synonym for pathologic ileus, because the intestinal musculature is not paralyzed. The ability of the smooth muscle to generate maximal force of contraction is unchanged in pathologic ileus. Neural influences actively inhibit the intestinal musculature and account for the prolonged absence of muscle contraction and motility seen in pathologic ileus. The way it starts and the prolonged nature of pathologic ileus are reminiscent of skeletal muscle reflex paralysis that is acutely associated with spinal cord injury and ensuing spinal shock. In spinal shock, the neural circuits of the spinal cord that normally mediate motor reflexes become nonfunctional for a transient period of time. In the case of pathologic ileus, the neural circuits of the enteric nervous system that normally initiate and organize propulsive motor behavior in the intestine become nonfunctional for a transient period. Although neural mechanisms are involved in both cases, the details of the neurophysiologic changes cannot be explained fully for either case.

 

Activation of sympathetic innervation is implicated in the initiation of pathologic ileus. Virtually all of the sympathetic nerve fibers, which enter the intestine outside of the sphincters, end in the ganglia of the enteric nervous system. Norepinephrine released from the sympathetic nerves acts to suppress the release of acetylcholine at the millions of nicotinic synapses that are part of the integrative neural networks of the enteric nervous system. This inactivates the neural circuits and thereby prevents them from activating propulsive motility. Subpopulations of enteric inhibitory motor neurons remain active in this circumstance and act to continuously suppress contraction of the inherently myogenic musculature.

Although sympathetic activation and the release and action of norepinephrine in the enteric nervous system are an attractive explanation for pathologic ileus, some observations do not support the hypothesis. For example, pretreatment with drugs that block the receptors for norepinephrine or that suppress its release from sympathetic nerves is ineffective for prevention of the ileus associated with laparotomy. Infiltration of the splanchnic innervation with a local anesthetic to block sympathetic nerve traffic to the intestine does not reverse the ileus seen during laparotomy in dogs. On the other hand, injection of a local anesthetic into the blood entering the intestine immediately evokes rigorous contractile activity. Two conclusions emerge from these observations. One is that activation of sympathetic reflexes may release substances other than norepinephrine that initially "lock" the integrated microcircuits of the intestinal enteric nervous system in a state of prolonged paralysis; this ensues for prolonged periods of time without further sympathetic input. The second conclusion is that ongoing activity of enteric inhibitory motor neurons accounts for the absence of contractile behavior. Blockade of the inhibitory neuronal activity by injection of a local anesthetic releases the muscle from the inhibition. Uncoordinated contractile activity appears after neural blockade due to the autogenic properties of the musculature.

## See Also the Following Articles

**Autonomic Innervation • Basic Electrical Rhythm • Colonic Obstruction • Disinhibitory Motor Disorder • Enteric Nervous System • Hirschsprung's Disease (Congenital Megacolon) • Intestinal Pseudoobstruction • Toxic Megacolon**

## Further Reading

Cullen, J., Carapreso, D., Hemann, L., Hinkhouse, M., Conklin, J., and Ephgrave, K. (1997). Pathophysiology of adynamic ileus. *Dig. Dis. Sci.* **42**, 731–737.

Summers, R., and Liu, C. (1995). Approach to the patient with ileus and obstruction. *In* "Textbook of Gastroenterology" (T. Yamada, D. Alpers, C. Owyang, D. Powell, and F. Silverstein, eds.), 2nd Ed., Vol. 1, pp. 796–798. J. B. Lippincott, Philadelphia.

Wood, J. (1999). "Neurogastroenterology and Motility." Milner-Fenwick, Timonium, Maryland.

# Pepsin

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**pepsin** Aspartic proteinase (36 kDa), derived from pepsinogen under acidic conditions; assists the digestion of dietary protein.

**pepsinogen** Proenzyme (40 kDa) synthesized and stored in zymogen granules and secreted by chief cells of the stomach.

**Pepsin, a protease present in the gastric lumen, is secreted by the chief cells of the gastric mucosa as an inactive precursor, pepsinogen; pepsinogen is activated by acid present in the gastric lumen, which initiates digestion of protein. Multiple genes code for immunologically distinct forms (isoenzymes) of pepsin, but all forms appear to have functional similarity. Peptic ulcers and acid-peptic disease derive their names from pepsin.**

## HISTORICAL OVERVIEW

In groundbreaking experiments using human gastric juice, the American physician/physiologist William Beaumont (1785–1853) hypothesized that, in addition to acid, an unknown factor contributed to protein digestion. The German physiologist Theodor Schwann (1810–1882) identified this factor from its ability to digest egg white and designated it "pepsin" (derived from the Greek word *pepsis*, for digestion). In England, using amphibian peptic cells as a model, the Cambridge physiologist John Langley (1852–1925) elucidated the formation of pepsinogen in chief cells, its storage in cytoplasmic zymogen granules, and, after secretion, its conversion to the active acid protease, pepsin. In 1930, John Northrop crystallized pepsin. Recent advances in structural biology have revealed how the three-dimensional structure of these molecules explains their activation and actions.

## STRUCTURE AND ACTIVATION OF PEPSIN

Like other aspartic proteinases (EC 3.4.23.X), pepsin (approximate molecular mass, 36 kDa) is synthesized as a proenzyme, pepsinogen (approximate molecular mass, 40 kDa), which is stable at neutral and alkaline pH ($>6$) and is converted to active pepsin at acid pH by proteolytic cleavage of an N-terminal prosegment (inhibitory piece). Studies of the crystal structure of pepsinogen indicate that the inhibitory piece shields the substrate-binding portion of the active protease, with six basic amino acids in the prosegment forming electrostatic interactions with acidic amino acids in pepsin. Thus, at neutral pH, the inhibitory piece maintains the enzyme in its inactive form by sterically blocking access to the active site and neutralizing negative charges in pepsin, thereby stabilizing the conformation of the proenzyme.

Exposure to acid results in protonation of carboxylate groups and repulsion of the net positive charges that disrupt the electrostatic interactions, unblocking the active site and activating the enzyme. Moreover, pepsinogen is subject to the proteolytic action of activated pepsin (autocatalysis). By these mechanisms, exposure to pH $<6$ (as expected in the gastric lumen) activates a rapid (2 sec at pH 5–6; 5 msec as the pH approaches 2) cascade of pepsin activation. Returning ambient pH to neutrality can arrest or reverse these conformational changes. Increasing the pH to $>7.2$ (as expected in the normal small intestine) or the temperature to $>65°C$ irreversibly denatures pepsin, whereas pepsinogen is stable to pH 10 and 100°C.

The molecular structure of human pepsin (Fig. 1) is very similar to that of other members of the aspartic proteinase family. The central hydrophobic core of pepsin (catalytic aspartic acid residues at position 32 and 215) comprises the active site of the enzyme. This site can accommodate an approximately 8-amino-acid portion of protein substrate.

## MEASUREMENT OF PEPTIC ACTIVITY

Measurement of peptic activity was first standardized by Anson and Mirsky in 1932; they defined 1 peptic unit as the activity of pepsin (pH 2, 37°C) that results in the release over 10 minutes of 0.1 μmol of tyrosine from 5 ml of 2% hemoglobin. To increase sensitivity and facilitate the analysis of multiple samples, investigators have modified this assay by using radiolabeled substrate (hemoglobin and albumin) and automated assays.

 

FIGURE 1 Schematic structure of human pepsin (EC 3.4.23.1), drawn according to coordinates deposited in the Protein Data Bank (identification number 1PSN). Light gray indicates β sheets; dark gray indicates α helices. The aspartic acid residues at positions 32 and 215 delineate the active site of the enzyme (in a ball-and-stick configuration).

Rather than using a defined absolute unit of peptic activity, many investigators express results as a percentage of peptic activity in experimental samples compared to control or, in secretory studies, as a percentage of total peptic activity in the sample.

## ACTIONS IN NORMAL PHYSIOLOGY AND DISEASE

The major function of pepsin is to initiate digestion of ingested proteins. The greater activity of pepsin for meat proteins, such as collagen, indicates that the enzyme is less important for hydrolysis of vegetable proteins. In addition, in neonates, pepsin may assist in milk clotting. The pH optimum for peptic hydrolysis of proteins depends on the substrate (pH 1.5–2.5 for hemoglobin, pH 3 for albumin, and pH 5.5 for milk clotting).

Peptic activity releases free amino acids and small peptides that can be absorbed by enterocytes lining the small intestine. Relatively large peptides resulting from incomplete pepsin digestion also enter the duodenum and are further degraded by pancreatic proteinases. Some products of peptic digestion also serve a signaling function because they stimulate the release from the distal stomach (gastrin) and duodenum of hormones (cholecystokinin-releasing peptide and others) that play additional roles in regulating digestion.

Pepsin appears to play a crucial, if not necessary, role in ulceration of the stomach and duodenum. In the absence of pepsin, gastric acid does not cause ulceration. Hence, major benefits of antacid therapy in the treatment of ulcer disease may be inhibition of the conversion of pepsinogen to pepsin and the maintenance of a gastric luminal pH greater than the optimum for the enzyme. Changes in the level or distribution of pepsinogen in blood and urine that are observed in peptic ulcer disease and gastric cancer have not proved clinically useful.

## See Also the Following Articles

**Chief Cells • Duodenal Ulcer • Gastric Acid Secretion • Gastric Ulcer • Protein Digestion and Absorption of Amino Acids and Peptides**

## Further Reading

Fujinaga, M., Chernaia, M. M., Tarasova, N. I., Mosimann, S. C., and James, M. N. (1995). Crystal structure of human pepsin and its complex with pepstatin. *Protein Sci.* **4**, 960–972.

Hershey, S. J. (1994). Gastric secretion of pepsins. *In* "Physiology of the Gastrointestinal Tract" (L. R. Johnson, ed.), 3rd Ed., pp. 1227–1238. Raven Press, New York.

Raufman, J.-P. (1996). Peptic activity and gastroduodenal mucosal damage. *Yale J. Biol. Med.* **69**, 85–90.

Sielecki, A. R., Fujinaga, M., Read, R. J., and James, M. N. (1991). Refined structure of porcine pepsinogen at 1.8 Å resolution. *J. Mol. Biol.* **219**, 671–692.

# Percutaneous Drainage

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abscess Collection of pus formed by tissue destruction in an inflamed area of a localized infection.
Seldinger technique Used for the insertion of a guidewire into a vessel.
tandem-trocar technique Used to cannulate into a vessel.

**Even though there has never been a debate about whether abscesses should be drained; the available options for drainage have changed. Traditionally, an operation has been required, whether a thoracotomy for empyema, or a laparotomy for diverticular abscess. The modern technique of image-guided percutaneous drainage has now become the first choice for many clinicians and patients. Surgery is increasingly reserved only for difficult-to-reach locations, for cases in which percutaneous drainage fails, or for cases in which urgent surgical exploration is needed in view of impending sepsis.**

## INDICATIONS, APPROACHES, AND GUIDANCE

Patients harboring intraabdominal abscesses usually present with signs of systemic inflammation, including fever, leukocytosis, and pain. Postoperative fluid collections represent the most common cause of intraabdominal abscess and are often localized to the dependent pelvis. Other common causes of pelvic abscesses include appendicitis, diverticulitis, and pelvic inflammatory diseases. Although most abscesses are drained transabdominally when possible, the pelvis represents a challenge due to obscuring bowel loops from ileus and the abundance of vascular structures. Alternative approaches of transrectal and transvaginal drainage guided by ultrasound as well as transgluteal drainage guided by computed tomography (CT) are employed routinely.

Liver abscesses are common and they can be either single or multiple. Single pyogenic abscesses are frequently located in the right lobe, whereas multiple abscesses occupy both lobes. Drainage of single abscesses can often be guided by ultrasound alone, but multiple abscesses typically require multiple drains and are CT guided. Subdiaphragmatic abscesses represent a challenging location and require a combination of imaging procedures for guidance.

Pancreatic fluid collections occur following episodes of acute pancreatitis. They can present early as pancreatic necrosis or late as symptomatic pseudocysts. CT is the usual method of drainage in these cases. Aspiration without catheter placement is not appropriate as the chance of recurrence approaches 70%.

## PROCEDURES

Before starting the procedure, it is important to ensure that drainage is clinically indicated, coagulopathy is corrected, and the imaging modality and the approach are chosen. Broad-spectrum antibiotics are usually given 1 hour preprocedure. The procedure is usually performed with a combination of intravenous conscious sedation (fentanyl, versed) and local anesthesia. A diagnostic scan is typically obtained with a radio-opaque skin marker.

Diagnostic aspiration with a 22-gauge needle will confirm the depth of the cavity as well as the path for catheter placement. The aspirate should be examined by gram stain and culture, although organisms may not be found if patients have been receiving antibiotics. White cells can be absent if patients are immunocompromised. In addition, the presence of creatinine suggests a urinoma, bilirubin suggests biloma, fat globules suggest lymphocele, and amylase suggests pseudocysts. Care is taken not to decompress the abscess cavity completely. The exchange of the aspiration needle for the catheter is done using the Seldinger technique or the tandem-trocar technique and a large catheter of 12- to 14-gauge lumen is left for drainage. There are many types of catheters. Pigtails are the most common types, and the drainage site is left in the dependent position if possible. After catheterization, the cavity is irrigated many times and, most importantly, the drain is secured externally. Finally, an additional scan is completed to ensure that there are no undrained collections.

Daily drain care and inspection are paramount. The usual recommendation for flushing is 5 ml, three or four times a day, to prevent clogging. When the catheter

 

drains less than 10 ml for a 24-hour period, it is usually reasonable to remove it, but it is important to confirm that the decrease in drainage is not secondary to blockage. Sudden decrease in drainage can be secondary to catheter obstruction. Imaging with either CT or a sinogram is important to demonstrate complete drainage.

## CLINICAL TRIALS

There is a lack of randomized clinical trials comparing surgical drainage to percutaneous drainage of abscesses. In a retrospective review of 32 patients with Crohn's disease who underwent percutaneous drainage from 1985 to 1999, there was a 95% success rate, with 50% of patients avoiding surgery in the short term (< 60 days). There was not any significant increase in need for surgery long term among those patients treated by drainage. The abscess recurrence rate of 22% was comparable to surgical drainage.

Although most retrospective studies of percutaneous drainage have shown promising results, one review of 160 unselected patients who underwent drainage of pancreatic pseudocysts revealed lower success (88 vs. 42%), higher mortality (16 vs. 0%), more complications (64 vs. 27%), and longer hospital stay (45 vs. 18 days) in the percutaneous drainage group.

## CATHETER COMPLICATIONS

In an older retrospective study on the use of percutaneous drainage in 118 patients from 1979 to 1984, there was a reported 4.2% major complication rate, which includes septic shock, hemorrhage, subphrenic abscess, and formation of an arteriovenous fistula, and a mortality rate of 2.5%. Other complications include the formation of an enteric fistula, which presents as a change in character and volume of the drainage.

## CONCLUSION

There is still some debate among authorities on surgical approaches and percutaneous drainage of abscesses, but the majority of patients who develop intraabdominal abscesses are now treated noninvasively. This approach has radically changed the surgical management of many patients and has allowed them to avoid an open surgical approach, which may increase their chances for other postoperative complications. The increasing use of and demand for guided percutaneous drainage will revolutionize the treatment of many surgical disorders as well as offer clinicians and their patients another less invasive option for drainage.

### See Also the Following Articles

Computed Tomography (CT) • Liver Abscess • Pancreatic Pseudocysts

### Further Reading

Gervais, D. A., Hahn, P. F., O'Neill, M. J., and Mueller, P. R. (2002). Percutaneous abscess drainage in Crohn disease: Technical success and short- and long-term outcomes during 14 years. *Radiology* 222(3), 645–651.

Hamlin, J. A, Friedman, M., Stein, M. G., and Bray, J. F. (1986). Percutaneous biliary drainage: Complications of 118 consecutive catheterizations. *Radiology* 158(1), 199–202.

Harisinghani, M. G., Gervais, D. A., Hahn, P. F., Cho, C. H., Jhaveri, K., Varghese, J., *et al.* (2002). CT-guided transgluteal drainage of deep pelvic abscesses: Indications, technique, procedure-related complications, and clinical outcome. *Radiographics* 22(6), 1353–1367.

Heider, R., Meyer, A. A., Galanko, J. A., and Behrns, K. E. (1999). Percutaneous drainage of pancreatic pseudocysts is associated with a higher failure rate than surgical treatment in unselected patients. *Ann. Surg.* 229(6), 781–787; discussion, 787–789.

Men, S., Akhan, O., and Koroglu, M. (2002). Percutaneous drainage of abdominal abscess. *Eur. J. Radiol.* 43(3), 204–218.

# Percutaneous Endoscopic Gastrostomy (PEG)

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**enteral** By way of the gastrointestinal tract.
**fluoroscopy** Examination of the tissues using an X-ray fluoroscope.
**gastrostomy** An opening into the stomach.
**ligament of Treitz** Suspensory muscle of the duodenum that anatomically divides the duodenum from the jejunum.
**parenteral** By means other than the gastrointestinal tract, such as via intravenous injection.
**volvulus** Twisting of the intestine, resulting in obstruction.

**The placement of a percutaneous endoscopic gastrostomy tube is a widely used method of delivering enteral nutrition to those unable to eat. The process involves inserting a thin tube through the wall of the abdomen into the stomach; the tube allows nutrient augmentation, fluid administration, or medication delivery. In properly selected patients, the procedure is safe, well tolerated, and successful in over 90% of individuals.**

## INTRODUCTION

As the population ages and life-sustaining technologies are advanced, many circumstances arise in which patients are unable to eat or tolerate oral intake. In this setting, additional means exist to provide nutrition, fluids, and medications, either by enteral or parenteral methods. When possible, enteral feeding is the preferred route to provide nutrition to patients with a functioning gastrointestinal (GI) system. By maintaining even a minimal exposure of nutrients to the enteral GI tract, there are significant benefits for the patient, including preserving the function of the enteral immune system, preventing mucosal atrophy, maintaining the normal gut flora, and reducing the incidence of sepsis. In addition, enteral nutrition is generally safer and less costly than parenteral nutrition. For short-term needs, nasoenteric feeding tubes are safe, effective, and easy to place and subsequently to remove. However, when oral intake will be compromised for an extended period of time, percutaneous endoscopic gastrostomy (PEG) tubes have become the delivery systems of choice. Introduced in the early 1980s, PEG tubes have several advantages over surgical gastrostomies. PEG tubes can be placed using only mild sedation and topical anesthesia and require less time compared to surgical gastrostomies, which are generally performed under general anesthesia. In addition, PEG tubes are less expensive and have fewer complications compared to surgical gastrostomies.

## INDICATIONS AND CONTRAINDICATIONS

In the adult population, the most common conditions that lead to PEG placement are neurologic disorders such as strokes, amyotrophic lateral sclerosis, neurologic trauma, and dementia. Other illnesses include head and neck cancers, facial trauma, and the short bowel syndrome. PEG tubes are most often placed for the purpose of providing long-term enteral nutrition. Other goals may include decreasing the risk of aspiration, improving survival, decreasing the risk of infection, and healing pressure ulcers. At times, PEG tubes are also placed to allow decompression of the stomach, such as in the setting of malignant intestinal obstruction or gastric outlet obstruction, often referred to as a "venting" PEG. Less common indications include treatment of gastric volvulus via fixation of the stomach to the anterior abdominal wall, and to allow access to the stomach for transgastric surgical instrumentation.

Absolute contraindications to PEG placement are the inability to advance the gastroscope, a limited life expectancy, or the inability to bring the gastric wall and anterior abdominal wall in apposition (which is required for proper healing and tract formation). The inability to transilluminate the anterior abdominal wall is considered by many to also be a contraindication to placement. However, there are data to suggest that with definite localization, with external palpation, and in the absence of air aspiration prior to needle visualization (see below), the technique can be performed safely. There are relative contraindications as well, including compromised wound healing, morbid obesity, massive ascites, coagulopathy, gastric varices, history of subtotal gastrectomy, peritoneal dialysis, portal hypertension, large hiatal hernia, hepatomegaly, and neoplastic or infiltrative disease involving the gastric wall.

 

## PEG INSERTION

The following description is a standard technique for placing PEG tubes. Prior to the procedure, intravenous antibiotics are typically administered to minimize infectious complications. An endoscope is passed through the mouth and esophagus and into the stomach. The stomach is insufflated with air to fully distend it. The room lights are lowered and through the use of external palpation of the anterior abdominal wall, combined with internal transillumination through the gastric wall, the site for PEG tube insertion is identified. This site is marked and then prepared with a cleansing solution and a sterile field is created. Local anesthetic is administered to this site. A small-caliber needle is inserted along the projected tube insertion tract for confirmation. The needle is slowly advanced in the direction of the stomach lumen while continuous negative pressure is being applied to the plunger. Endoscopic visualization of the needle tip as it pierces the gastric wall must coincide with aspiration of air back into the syringe. Aspiration of air bubbles prior to endoscopic visualization of the needle suggests the penetration of an interposed hollow viscus (e.g., colon) and should prompt immediate removal of the needle. Once the direct tract of the PEG tube has been confirmed in this manner, a skin incision approximately 1 cm in length is made to allow passage of a trochar. The trochar is passed through the skin incision into the stomach and a flexible guidewire is advanced through the trochar. A snare is then passed through the endoscope into the stomach. The snare is opened and manipulated to secure the end of the guidewire. The scope, snare, and guidewire are then withdrawn through the mouth as a single unit.

At this point in the procedure either a "pull" or "push" technique can be performed. Both methods have similar success rates, and choice is based on operator preference and experience. Using the pull technique, a loop on the most proximal end of PEG tube is tied to the end of the guidewire that was withdrawn through the mouth. The tube is generously lubricated and the guidewire with the attached PEG is "pulled" back through the mouth into the stomach from the site of the skin incision. The tapered tube passes through the stomach wall and emerges through the premade skin incision. Traction is applied until gentle resistance, caused by an internal bumper attached to the distal end of the tube, is felt. Once mild resistance is met, the PEG tube is secured in place with an external bumper. Tube markings (in centimeters) indicate the distance between the internal and external bumpers. This distance, which is typically between 3 and 6 cm, is recorded. Usually, the endoscope is reinserted to visualize the internal bumper, in order to verify that there is the appropriate amount of traction on the tube, although this step is not required. A topical antibiotic ointment is applied to the skin site and the area is dressed and bandaged. The superfluous external portion of the PEG tube is trimmed to a workable length. An abdominal binder is applied to help keep the tube in place and minimize the risk of inadvertent tube removal while the tract matures. The push technique differs in that the tube has a central lumen, through which the guidewire is passed. The tube is "pushed" over the guidewire and advanced until it emerges through the skin surface. It is then secured in a manner similar to that used in the pull technique. A less commonly performed alternative to the push and pull techniques is the direct placement method, which uses a trochar with a peel-away surface that delivers the PEG tube and internal bumper into the stomach lumen, obviating the need to use a guidewire.

## PERCUTANEOUS ENDOSCOPIC JEJUNOSTOMY

Clinical scenarios occur when enteral nutrition delivered directly to the small bowel is indicated, and a PEG tube will not suffice. Direct percutaneous endoscopic jejunostomy (PEJ) tubes are an available option for enteral access in these situations. Indications for PEJ tubes include patients who have undergone gastric resection or have gastric outlet obstruction, gastric dysmotility, or a nonfunctioning gastrojejunostomy, or patients at significant risk for aspiration events. PEJ tubes are placed in a manner similar to that of PEG tubes. A push enteroscope, which is longer than the standard upper endoscope, is used and passed into the jejunum beyond the ligament of Treitz. As with PEG insertion, transillumination of a loop of small bowel must be achieved followed by the insertion of a feeding tube into the jejunum, using the technique described for PEG placement. The tubes used for PEJs are those found in standard PEG kits. Fluoroscopy or a combined approach with a gastroenterologist and radiologist is often used to facilitate the placement of PEJ tubes. Although the procedure is more technically demanding, the success rate is comparable to that of PEG placements. Direct PEJ tubes should be differentiated from jejunal tubes that are placed through gastrostomy or PEG tubes (the so-called JET-PEG). These tubes are often used for indications similar to those for direct PEJ tubes, but it has been shown that the jejunal portions of these tubes tend to migrate back into the stomach, essentialy rendering them a PEG tube.

## COMPLICATIONS

PEG placement is generally a safe and well-tolerated procedure. The procedure has an associated mortality rate of approximately 1%, with major complications occurring in 2.5–3% of cases. Complications can be divided into major and minor categories. Major complications include perforation, peritonitis, aspiration, gastrocolocutaneous fistula, necrotizing fasciitis, and premature device dislodgment. Minor complications include peristomal wound infection, which is the most common complication. Antibiotic prophylaxis with 1 g of cephazolin 30 minutes prior to the procedure is recommended to reduce the incidence of this complication. Additional minor complications include tube malfunction or clogging, leakage around the tube site, and migration of the tube. Less common complications also include implantation or seeding of tumor cells at the PEG tube site, aortogastric fistula, and gastric volvulus.

## ETHICAL CONSIDERATIONS

It is unfortunate that most patients in need of a PEG tube are severely debilitated and often near the end of life. Because of this, PEG use has often been the subject of charged ethical debate. In a difficult and emotional setting such as this, it is essential that the goals of the intervention are clear, and the risks and benefits thoroughly considered. Although there are many currently accepted indications for PEG placement, very few data are available to directly support its use, despite being a commonly performed procedure for over 20 years. A keen example is the use of PEG tubes to reduce the risk of aspiration pneumonia. Although direct instillation of nutrients into the stomach obviates problems with swallowing food, to date, there have been no trials that conclude either PEG or PEJ tubes reduce the risk of aspiration. Enteral feeding tubes will not eliminate aspiration of oropharyngeal secretions, a common and recurrent cause of aspiration. Further, it has been suggested that PEG tubes can actually increase the amount of gastroesophageal reflux, a risk factor for aspiration, by altering the gastroesophageal angle. Similar to the case for aspiration, there are few data to support PEG use to decrease mortality, improve wound healing, or improve markers of nutrition. These areas deserve further study.

When the benefit of a procedure is in question, the risks of the procedure must be carefully examined. PEG, although generally accepted as a safe procedure, does carry risks of morbidity and even mortality, as previously described. In several large studies, the 1-year mortality rate after PEG placement was greater than 50%. In this severely ill population, alternative noninvasive approaches should always be presented. Postprocedural ethical issues also need to be considered. These include the fact that often physical and chemical restraints need to be used in order to prevent confused or agitated patients from pulling out the tube, with the attendant complications. Additionally, when PEG feedings are to be used on a trial basis, the end points for discontinuing PEG use, such as duration and improvement in clinical parameters, should be clearly set prior to placement. All patients or their surrogates should be fully informed of the potential benefits, risks, and alternatives to PEG placement.

## CONCLUSION

Since its description as an alternative to open gastrostomy, PEG tube placement has become a common endoscopic procedure. A pragmatic understanding of the realized benefits of PEG placement and enteral feeding, as well as the risks, by both the health care team and patient, is an essential first step in the process. In the future, technological advances, combined with responsible patient selection, will optimize the use of the PEG procedure for optimizing delivery of enteral feeding in various clinical settings.

### See Also the Following Articles

**Enteral Nutrition • Gastric Outlet Obstruction • Gastric Surgery • Gastrostomy • Parenteral Nutrition • Volvulus**

### Further Reading

Feldman, M. (1998). "Sleisenger & Fordtran's Gastrointestinal and Liver Disease." W. B. Saunders, Philadelphia, PA.

Finucane, T., Christmas, C., and Travis, K. (1999). Tube feeding in patients with advanced dementia: A review of the evidence (1999). *JAMA* 282(14), 1365–1370.

Ginsberg, G., Bosco, J., Barkun, A., *et al.* (2002) Endoscopic enteral nutritional access devices. *Gastrointest. Endosc.* 56, 796–802.

Safadi, B., Marks, J., and Ponsky, J. (1998). Percutaneous endoscopic gastrostomy. *Gastrointest. Endosc. Clin. North Am.* 8, 551–563.

Schapiro, G., and Edmundowicz, S. (1996). Complications of percutaneous endoscopic gastrostomy. *Gastrointest. Endosc. Clin. North Am.* 6, 409–422.

# Percutaneous Transhepatic Cholangiography (PTC)

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**choledochocele** Cystic biliary dilatation within the wall of the duodenum.

**choledochoenterostomy** Anastomosis created between bile duct and intestine. The most commonly performed anastomosis is between bile duct and jejunostomy (Roux-en-Y) because it eliminates biliary reflux of food material.

**endoscopic retrograde cholangiopancreatography** Visualization of the bile ducts and pancreatic duct, achieved by injecting iodinated contrast medium through an endoscope into the biliary and pancreatic ducts in a retrograde manner.

**magnetic resonance cholangiopancreatography** Visualization of the bile ducts and pancreatic duct, achieved during magnetic resonance imaging; does not require contrast medium to be injected into the ducts. The ducts are visible because of differences between the magnetic properties of the biliary/pancreatic fluid and surrounding tissues.

**percutaneous transhepatic cholangiography** Visualization of the intrahepatic and extrahepatic bile ducts, achieved by injecting iodinated contrast medium into the bile ducts. Injection is done by passing a needle and catheter through the abdominal wall, through the liver capsule, and into the bile ducts. Percutaneous access to the bile ducts also allows the operator to perform biliary tract interventions such as percutaneous biliary drainage.

**portoenterostomy** Surgical treatment (Kasai) procedure for extrahepatic biliary atresia. A Roux-en-Y limb is anastomosed to the dissected fibrous biliary plate on the undersurface of the liver.

**Percutaneous transhepatic cholangiography (direct injection of iodinated contrast medium into the bile ducts under fluoroscopy) is a method of imaging the bile ducts with contrast medium. Prior to the emergence of endoscopic retrograde cholangiopancreatography (ERCP), which involves injection of contrast medium into the biliary tree endoscopically through the ampulla of Vater, percutaneous transhepatic cholangiography (PTC) was the sole means of imaging the bile ducts with contrast medium. Currently, because ERCP is less invasive than PTC for obtaining a cholangiogram, it is the method of choice in medical centers that are staffed by endoscopists who are adept at the procedure. Cholangiography obtained by injection of iodinated contrast medium into the bile ducts during ERCP or PTC is considered to be the gold standard for bile duct imaging.**

## INDICATIONS FOR PTC

Computed tomography (CT), ultrasound (US), and magnetic resonance cholangiopancreatography (MRCP) have emerged over the past two decades as noninvasive means of viewing the bile ducts. These modalities do not require injection of iodinated contrast into the bile ducts. However, current technical limitations make the bile duct detail obtained with these imaging methods inferior to that obtained with PTC and ERCP. This is particularly true for visualization of the subsegmental bile ducts.

PTC is indicated for the following reasons:

1. To determine the level of biliary obstruction and to attempt to categorize the lesion as benign or malignant.
2. For preoperative delineation of bile duct anatomy. In this case, it is important to demonstrate the amount of normal bile duct above an obstruction for planning a choledochoenterostomy and also for excluding the presence of variant biliary anatomy.
3. To determine if a biliary stricture is present in the patient with normal-caliber bile ducts on cross-sectional imaging and to assess clinical and laboratory evidence of biliary obstruction. This scenario is most often encountered in the postoperative patient (biliary bypass, partial liver resection, orthotopic liver transplant) who has undergone choledochoenterostomy.
4. To provide a percutaneous transhepatic tract for future percutaneous interventions, such as bile duct biopsy, stone removal, balloon dilatation of a biliary stricture, or placement of a permanent metallic stent across a nonoperable malignant biliary occlusion.

 

## PREPROCEDURE WORKUP

The patient has usually had a CT scan, abdominal magnetic resonance imaging (MRI), MRCP, or liver ultrasound prior to PTC. When obstructive cholangitis is suspected, these studies will have supplied information about the presence or absence of bile duct dilatation, obstructing mass, gallstones, biliary strictures, collections of bile, and ascites. Bile collections related to bile leak are drained percutaneously under CT or ultrasound guidance before PTC. When the presence of biliary pathology is suggested on these studies, ERCP is usually performed next to provide information about the bile ducts with an iodinated contrast cholangiogram. ERCP is associated with less risk than PTC and obviates the need for PTC if technically successful. ERCP can be unsuccessful because of: postoperative anatomy (Roux-en-Y), difficulty passing the endoscope through the duodenum because of a duodenal stricture related to pancreatitis or tumor, inability to visualize or cannulate the ampulla of Vater because of duodenal stricture or tumor, and inability to achieve an adequate level of sedation.

When PTC becomes necessary, informed consent is obtained from the patient or guardian. General anesthesia is arranged for the pediatric patient or the adult patient in whom an adequate level of conscious sedation cannot be achieved. Antibiotics are administered intravenously. Coagulation and platelet count abnormalities are corrected to as near normal as possible. Vital signs are monitored throughout the case. The patient is given corticosteroids prior to the procedure if an allergy to iodinated contrast exists.

## TECHNIQUE

A radiologist performs PTC in the interventional suite of the department of radiology. A dedicated interventional radiology nurse administers conscious sedation and monitors vital signs throughout the procedure. The patient is placed prone on a fluoroscopy table in a room outfitted with a multiangle image intensifier. The abdomen is prepped and draped in sterile fashion from the level of the nipples to the umbilicus. A 22-gauge Chiba needle is passed into the liver under fluoroscopic guidance. The stylet is withdrawn and contrast is injected through the needle while the needle is retracted slowly. The operator stops retracting the needle when contrast flows into a bile duct. Several milliliters of contrast are injected into the ductal system. A 0.018-inch-diameter guidewire is advanced through the needle into the duct. The needle is replaced with a #3 French catheter with multiple side holes. The potentially infected bile is aspirated and sent to the microbiology laboratory for culture. Contrast is then injected into the ducts to obtain a diagnostic cholangiogram. Radiographic images of the opacified bile ducts are exposed from anterior–posterior, in the right-anterior oblique and left-anterior oblique directions, in order that the total extent of each duct can be evaluated.

For percutaneous access to the right hepatic biliary tree, the needle is passed into the right hepatic lobe at the junction of the lower and middle thirds of the liver. The needle is directed toward the left shoulder. For percutaneous access to the left hepatic lobe, the needle is passed into the ventral duct of the left biliary tree under sonographic guidance. Entry to the left biliary tree is usually made through a window between the left costal margin and the xiphoid process.

Unusual means of accessing the bile ducts sometimes become necessary. The gallbladder can be injected with contrast to fill the biliary tree in a retrograde fashion via the cystic duct. This method can only be used if the patient has a gallbladder and a patent cystic duct with free communication of the cystic duct with the extrahepatic and intrahepatic ducts. In patients with massive ascites and dilated bile ducts, the ductal system can be accessed by passing a needle system through the right internal jugular vein, through the right atrium, into inferior vena cava, and into the middle hepatic vein. The needle is then passed through the wall of the middle hepatic vein, through liver parenchyma, and into the biliary tree. Iodinated contrast medium is then injected through the needle system.

After diagnostic cholangiography is performed, the decision whether to intervene percutaneously is made. Interventions include bile duct biopsy, biliary drainage, balloon dilation of a benign stricture (Fig. 1), and placing an endobiliary stent (Fig. 2). This decision is often made in conjunction with the surgical and medical services.

## COMPLICATIONS

Complications occurring during PTC vary with the degree of technical difficulty experienced during the procedure. Patients with obesity, coagulopathy, comorbidities, sepsis, presence of ascites, and nondilated bile ducts are at increased risk. Complications include biliary sepsis, bile ascites, hemobilia, hemorrhage, and pneumothorax.

## INTERPRETATION

### Biliary Obstruction

Most cases of biliary obstruction are related to calculi or neoplasm. The most common tumors are

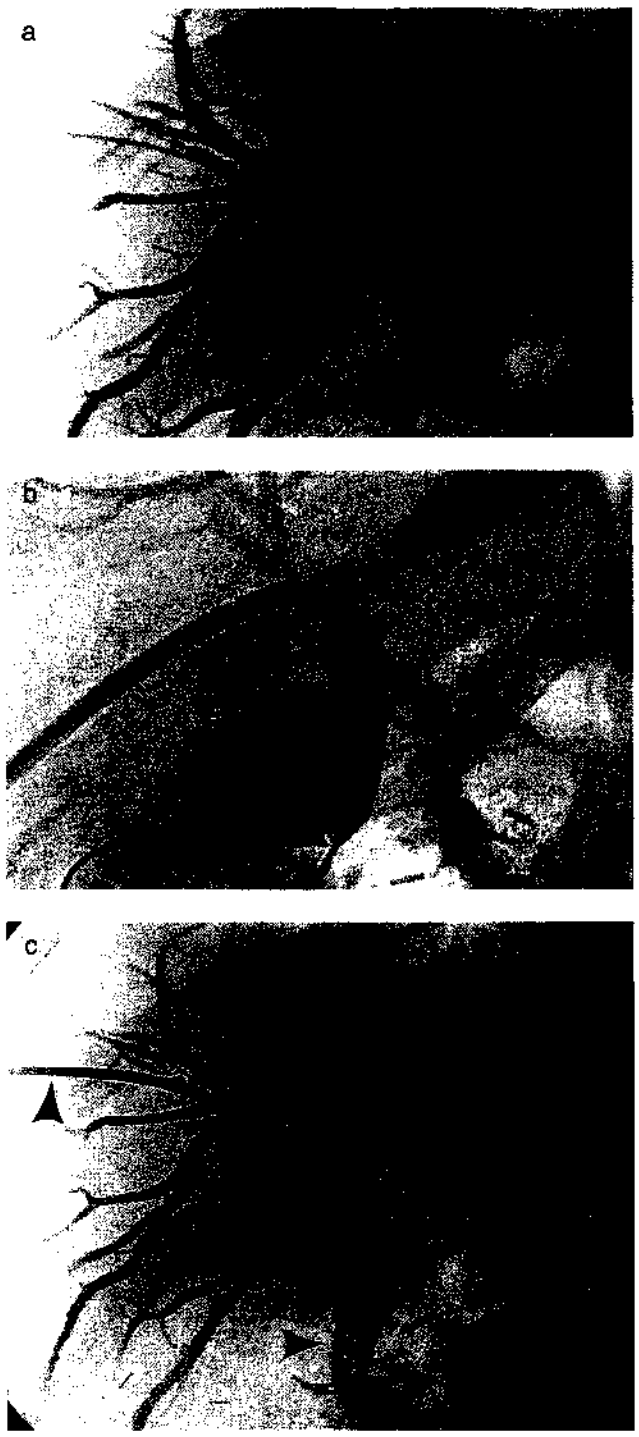


**FIGURE 1** (a) Benign anastomotic stricture (arrowhead) developed 13 months following creation of an anastomosis between the common hepatic duct and the jejunum. (b) A waist can be seen while dilating the stricture percutaneously with a 10-mm-diameter balloon. (c) A biliary drainage catheter (#8 French; arrowheads) with multiple side holes is kept in place for 6 weeks postprocedure, allowing drainage of bile across the anastomosis.

pancreatic cancer (Fig. 3) and metastatic disease (Fig. 4), followed by cancer of the bile ducts (Fig. 5), ampulla, and gall bladder. Less common causes of biliary obstruction include congenital biliary obstruction, bile duct injury, pancreatitis, sclerosing cholangitis, biliary atresia, choledochal cyst, duodenal diverticulum, infection, and parasitic infestation.

Biliary atresia is the most common cause of obstructive jaundice in infancy. It can involve the intrahepatic or extrahepatic bile ducts, the latter being more commonly involved and found in 1/10,000–1/15,000 births. Hepatic biliary scintigraphy suggests the diagnosis if there is a delay of radiotracer excretion into the gastrointestinal tract. Treatment for extrahepatic biliary atresia is surgical. A portoenterostomy (Kasai procedure) is performed. Liver transplantation is considered for the patient who has a failed Kasai procedure or for whom the diagnosis of biliary atresia was made late.

Choledochal cysts are seen in 1/13,000 hospital admissions in the United States. Three-quarters of affected patients are female. Theories for the pathogenesis of choledochal cysts include (a) anomalous pancreatobiliary duct junction, (b) abnormal canalization of the bile ducts, and (c) abnormal autonomic innervation of the extrahepatic bile duct. Todani's classification of choledochal cyst disease is most widely used. Type I cysts are extrahepatic and are seen in 80–90% of all cases. These can be focal or fusiform. A type II cyst is a diverticulum of the extrahepatic duct and is seen in 3% of cases. Type III is a choledochocele, seen in 5% of cases. Type IV cysts account for 10% of cases and are subdivided into two groups; type IVA is characterized by dilatation of the intrahepatic and extrahepatic biliary tree, and type IVB cysts are multiple extrahepatic cysts. Type V cysts, known as Caroli's disease, are intrahepatic and rare. Complications of choledochal cysts include biliary obstruction, cholangitis, rupture, hepatic abscess, and cancer of the bile ducts or gallbladder. Complete excision of the cyst is recommended because of the associated risk of cancer. In patients with pancreatitis, long segment narrowing of the common bile duct (CBD) can be seen, with gentle tapering distally. The entire CBD may be involved and the ampullary segment may be normal.

Primary sclerosing cholangitis (PSC) is a progressive disease of the biliary tree characterized by inflammatory and fibrotic bile duct lesions. The etiology of the disease is unclear. Patients often present with recurrent episodes of fever, chills, weight loss, pruritus, jaundice, and mild right upper quadrant discomfort. Laboratory tests usually reveal an elevated white blood cell count and a cholestatic biochemical profile. Histologic

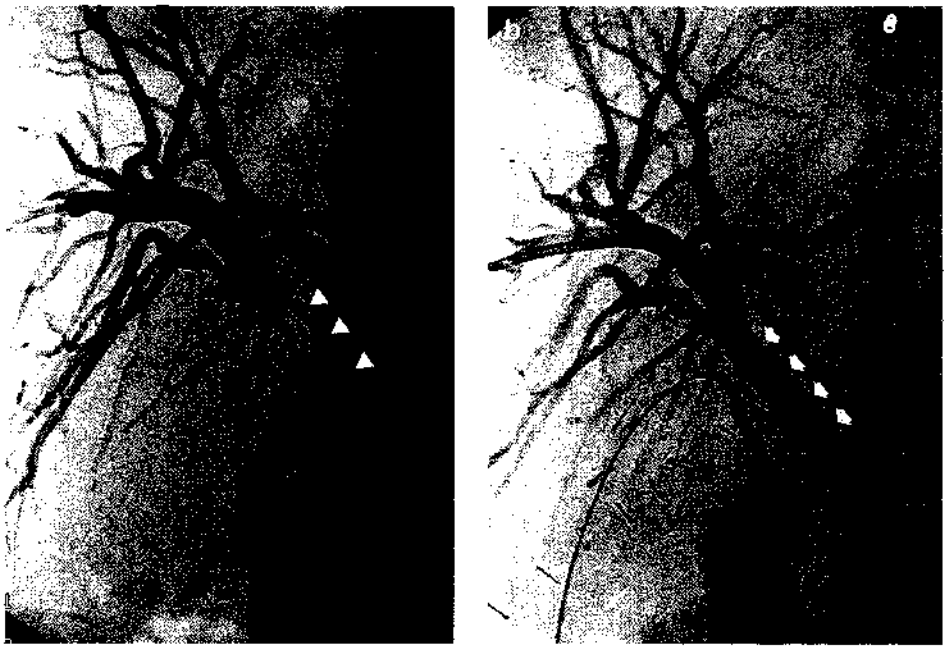


FIGURE 2 (a) A biliary drainage catheter (#8 French) with multiple side holes (arrowheads) traverses a long-segment malignant biliary occlusion. (b) A 10-mm-diameter stent (arrows) was positioned across the malignant occlusion to allow internal drainage of bile across the lesion. The percutaneous access was removed.

findings on liver biopsy are often nonspecific. The disease course is usually progressive, resulting in cholestatic liver disease. Cholangiography is a key component in making the diagnosis of PSC. Abnormalities of intrahepatic and extrahepatic bile ducts are seen in 75–80% of the patients. Isolated involvement of either the intrahepatic or extrahepatic ducts occurs in 10–20% of cases. Cholangiographic findings include focal narrowings, beading, pseudodiverticula, and pruning of intrahepatic duct branches. Long segment bile duct narrowing is not uncommon. However, brush cytology of dominant bile duct strictures should be performed because of the development of cholangiocarcinoma in 40% of the patients.

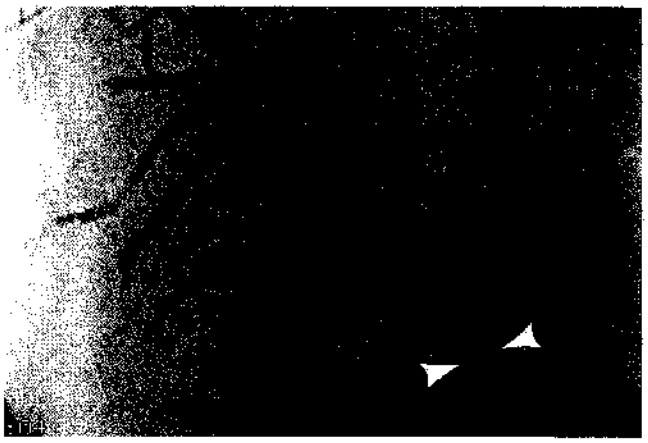

FIGURE 3 Abrupt termination (arrowheads) of the common bile duct is seen in a patient with pancreatic carcinoma.

Several disease processes can mimic PSC on cholangiography. These include metastatic disease to the liver, lymphoma, cholangiocarcinoma, cirrhosis, hepatic arterial chemotherapy, graft-versus-host disease, chronic allograft rejection, opportunistic infection of the bile ducts, multiple liver abscesses, systemic fungal disease, and ischemic bile duct strictures related to hepatic arterial compromise following hepatobiliary surgery or transplantation. Chronic biliary obstruction from gallstones or biliary strictures or chronic reflux of intestinal contents across biliary–enteric anastomoses can cause bacterial infection of the biliary tree, resulting in secondary cholangitis. These entities can be differentiated from PSC after careful history taking and review of hepatobiliary imaging and laboratory blood tests.

Common duct stones (Fig. 6) are seen in approximately 15% of patients with cystic duct stones. Retained stones in the biliary tree are present in 4% of patients who undergo cholecystectomy for gallbladder calculi. Bile duct calculi can also be seen in the setting of cholestasis related to intrahepatic or extrahepatic bile duct strictures (Fig. 7). Stones in the biliary tree are usually removed through an endoscopic approach. They are removed by a percutaneous transhepatic approach

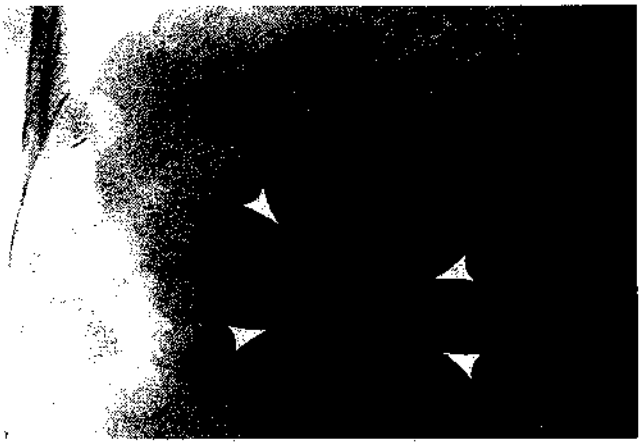

FIGURE 4 Colon carcinoma involving the portal lymph nodes creates a mass defect (arrowheads) on the common hepatic duct and the anastomosis of the common hepatic duct with the jejunum.

when the endoscopist is unable to access the biliary tree, usually in the setting of postoperative biliary anatomy. The diagnosis of biliary calculi is usually made by a noninvasive imaging method such as ultrasound or MRCP. Fifteen percent of gallstones are radio-opaque. On cholangiography, radio-opaque gallstones appear as well-defined filling defects. They are differentiated from tumors by their mobility within the ducts. Occasionally, an inflammatory reaction in the adjacent bile duct wall may cause them to be fixed, simulating a tumor. Contraction of the sphincter of Oddi can mimic the presence of a gallstone in the distal CBD. It can be difficult to differentiate gallstones from air bubbles and blood clots.

FIGURE 5 Cholangiocarcinoma (Klatskin tumor) involves the convergence of the right anterior sectoral duct (curved arrow), the left main hepatic duct (arrowhead), and the common hepatic duct (open arrows). The right posterior sectoral duct is completely occluded and does not fill with contrast.

Air bubbles coalesce, can be aspirated, and collect in anterior bile ducts. Blood clots usually clear after several days of biliary drainage.

Benign bile duct strictures are usually short. They may develop following hepatobiliary surgery, either as an iatrogenic injury to the duct or as anastomotic stricture following surgical creation of a choledochoenteric communication. When increased in length, benign biliary strictures are usually smooth and taper gradually. Cholangiographic features suggestive of cancer of the bile ducts, pancreas, or ampulla include abrupt termination of the bile duct, "apple core" concentric narrowing of the bile duct, and changes in caliber along the length of the stricture. Tumors can extend from the wall into the lumen of the bile duct in an exophytic fashion. Cross-sectional imaging often helps in making the diagnosis of malignancy. Brush biopsy of the biliary stricture or surgical exploration may be necessary to differentiate between benign and malignant lesions.

## Bile Duct Leak

Bile duct injury can develop during cholecystectomy, partial liver resection, slippage of clip or ligature from the cystic duct following cholecystectomy, PTC, liver biopsy, and blunt or sharp abdominal trauma. Drainage catheters are usually placed into

FIGURE 6 Oval filling defect (arrowhead) in the distal common bile duct represents a gallstone.

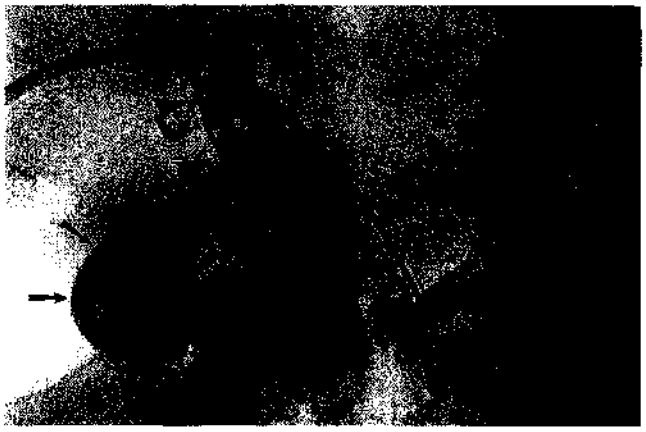

**FIGURE 7** Multiple filling defects represent gallstones in the common hepatic duct (arrowheads) and gallbladder (arrows).

bile collections under CT or US. ERCP is usually successful at demonstrating a cystic duct leak or leakage from a partially or completely lacerated bile duct. PTC becomes necessary when ERCP is unrevealing or technically unsuccessful. PTC is difficult in this patient group because the decompressed bile ducts are difficult to access with a needle and subsequently to cannulate.

Aberrant extrahepatic bile ducts are at risk for injury during operation because the surgeon may not anticipate their presence. PTC may demonstrate an aberrant right hepatic duct that was torn intraoperatively and no longer communicates with the biliary tree. This torn aberrant bile duct may go unappreciated on ERCP if a vascular clip is placed on the stump of the transected bile duct that arises from the main biliary tree. In this case, the radiologist passes a catheter percutaneously into the aberrant bile duct, allowing the surgeon to identify this transected duct intraoperatively for anastomosis of the duct to jejunum.

## See Also the Following Articles

**Bile Duct Injuries and Fistulas • Cholangiocarcinoma • Computed Tomography (CT) • Gallbladder Cancer • Gallstones, Pathophysiology of • Magnetic Resonance Imaging (MRI) • Pancreatic Ductal Adenocarcinoma • Radiology, Interventional • Ultrasonography**

## Further Reading

Clavien, P. A., and Baillie, J. (eds.) (2001). "Diseases of the Gallbladder and Bile Ducts." Blackwell Science, United Kingdom.

Meyers, W. C., and Jones, R. S. (eds.) (1990). "Textbook of Liver and Biliary Surgery." J. B. Lippincott, Philadelphia.

Pitt, H. A., Carr-Locke, D. L., and Ferrucci, J. T. (eds.) (1995). "Hepatobiliary and Pancreatic Disease: The Team Approach to Management." Little, Brown and Company, Boston.

Shlansky-Goldberg, R., and Weintraub, J. (1997). Cholangiography. *Semin. Roentgenol.* XXXII, 150–160.

# Perforation

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**angularis** Angular "notch" in the stomach that demarcates the division between the body and antrum of the stomach.
**diathermy** Local elevation of temperature within the tissues, produced by high-frequency current, ultrasonic waves, or microwave radiation.
**diverticulum** Pouch or sac opening from a tubular structure or saccular organ such as the gut or bladder.
**perforation** Abnormal opening in a hollow organ or viscus.

**Perforation is defined as an abnormal opening in a hollow organ or viscus. It is derived from the Latin *perforatus*, meaning "to bore through." Perforation is one of the most common etiologies of surgically treatable abdominal pain.**

## INTRODUCTION

Abdominal pain is a leading cause of hospital admission and physician visits. The severity ranges from benign self-limiting etiologies to life-threatening surgical emergencies. Subtle differences in the presentation cause this to be a very complex diagnostic dilemma. A thorough systematic evaluation is required for significant abdominal pain. Consequently, abdominal pain presents a universal challenge that transcends a wide spectrum of medical and surgical specialties.

Most abdominal pathology presents with associated abdominal pain. A complete understanding of the pathophysiology coupled with this abdominal pain is essential in the recognition of disease. Visceral, parietal, and referred pain are the commonly acknowledged divisions. The onset, quality, duration, location, and associated symptoms classify the pain. Visceral pain is perceived via autonomic nerve fibers (sympathetic/parasympathetic), which symmetrically innervate abdominal organs. As a consequence of this symmetry, the sensory perception is along the midline. Visceral pain is characterized as intermittent, deep, dull, aching, crampy pain associated with nausea and diaphoresis. Stimuli on the visceral organs include stretching/traction, compression, torsion, and chemicals. Somatic (parietal) pain is perceived via spinal nerves ipsilaterally innervating the body wall. Greater localization is achieved for this severe, persistent, sharp, stabbing pain that results from local inflammation and irritation. Referred pain typically arises from visceral organs, travels via sympathetic visceral nerve fibers, and is perceived in a location remote from the site of pathology. This double innervation is a consequence of common embryonic origin. Common examples include back pain resulting from pancreatitis, right shoulder pain from hepatobiliary disease, and left shoulder pain secondary to splenic pathology.

The initial evaluation of the acute abdomen begins with a complete history and physical, and continues with inspection, auscultation, and palpation. Nausea, vomiting, fever, chills, constipation, diarrhea, and natural history/quality/distribution of symptoms are important historical facts. Distension on inspection and decreased bowel sounds on auscultation are consistent with acute abdominal pathology. On palpation, guarding/rigidity, diffuse or point tenderness, and rebound tenderness can be observed.

Abdominal pain can arise from an array of varied etiologies presenting in a similar fashion. Subtle differences in the history, presentation, evaluation, and diagnostic workup guide the clinician. Nonsurgical pathology can mimic surgical disease. The clinician must consider nonsurgical pathology (gastroenteritis, acute hepatitis/pancreatitis, sickle cell crisis, lead toxicity, acute porphyria, or pneumonia) when considering potential surgical emergencies. Surgical disease can be further subdivided into nonperforated (acute cholecystitis) and perforated (duodenal ulcer) pathology. The commonly encountered gastroenteral perforations are presented here.

## PERFORATED ESOPHAGUS

Esophageal perforation is not typically considered a cause of abdominal pain. However, in order to complete the discussion of gastroenteral perforation, esophageal perforation is briefly considered. Esophageal perforation is a surgical emergency requiring rapid diagnosis. It most commonly occurs as a result of instrumentation, trauma, spontaneous perforation, and swallowing of a foreign body. It presents with pain in the cervical area,

 

dysphagia, and odynophagia. Symptoms are notably exacerbated with swallowing or movement. A recent history of instrumentation or vomiting is usually noted. Diagnostic workup includes posteroanterior and lateral chest films with findings of mediastinal emphysema/widening, cervical emphysema, or pneumothorax. Barium esophagram in the right lateral decubitis position is the gold standard for evaluation. Computed tomography and endoscopy have a limited role in the presence of an esophagram, but may be useful in complicated cases with equivocal studies. Treatment objectives include limitation of extravasation, prevention of infection, nutritional maintenance, and restoration of structural integrity. Nonoperative treatments offer a limited role in isolated cases. Operative exploration, wide drainage, and primary closure within 24 hours (if possible) remain the treatments of choice. Outcomes are variable and are contingent on duration to diagnosis and treatment, cause and location of injury, comorbidities, and existing esophageal disease.

## PERFORATED GASTRIC ULCER

Gastric ulceration often presents with acute-onset epigastric pain that radiates to the back and is exacerbated by the ingestion of food. Common risk factors include use of nonsteroidal antiinflammatory drugs (NSAIDs), cigarette smoking, and chemotherapeutic agents (5-fluorouracil, cisplatin, doxorubicin, or mitomycin C). Gastric ulcer disease presents in approximately 100,000 new cases annually and is most commonly seen in men and the elderly. Complications of gastric ulceration result in several thousand deaths and a 10% rate of gastric malignancy annually. Normal or decreased levels of acid secretion are observed with a breakdown in the gastric mucosal barrier. Ulceration is most common along the lesser curvature of the stomach at the junction between the antral and fundic mucosa. Of ulcers, 70% occur superior to the incisura angularis and 20% are distal. Gastric ulcers are classified into five categories defined by location and secretory status.

The gold standard for the evaluation of gastric ulceration is endoscopy. Treatment options include medical, endoscopic, and surgical management. Initial medical management includes antimicrobials directed at *Helicobacter pylori* (isolated in 85–90% of gastric ulcers) and antisecretory medications. Typically, a 12- to 24-week trial is undertaken. Endoscopic diathermy or vasoconstrictive injection can treat or temporize active bleeding. However, surgical management is indicated in cases complicated by nonhealing/recurrent ulcers, suspected malignancy, obstruction, hemorrhage (most common), and perforation.

Several surgical treatment options exist. Typical treatment includes excision of the lesion, a vagotomy, and a drainage procedure. The lesion should be excised if possible. Truncal or proximal gastric (highly selective) vagotomy is performed to limit acid secretion. Truncal vagotomy is undertaken at the level of the diaphragm as the vagal nerve fibers enter the abdomen. It is associated with a greater reduction in acid secretion and a lower recurrence rate compared to proximal gastric vagotomy. However, the gastric drainage mechanism and vagally supplied viscera are denervated and impaired. Thus, a gastric drainage procedure is mandatory with truncal vagotomy. However, antral nerve fibers (and gastric drainage) are preserved in cases of proximal gastric vagotomy. Unfortunately, this comes at the expense of a higher recurrence rate and greater acid secretion.

Drainage procedures include pyloroplasty and antrectomy. Several different types of pyloroplasty procedures are performed to improve drainage. However, each utilizes a longitudinal incision at the pylorus that is horizontally closed. Antrectomy is the resection of the distal stomach and removal of the pylorus. The defect can be repaired with a gastroduodenostomy (Billroth I) or gastrojejunostomy (Billroth II). Complicated proximal gastric ulceration may require a subtotal gastrectomy, whereas widespread gastric disease may require a near-total gastrectomy or gastric devascularization. These latter procedures are often associated with a very high morbidity and mortality and represent less commonly employed techniques. Following gastric drainage procedures or gastric resection, postgastrectomy syndromes can emerge. Early and late dumping, afferent and blind loop obstruction, alkaline reflux, gastric atony, and nutritional disturbances are all well-described complications of gastric surgery.

## PERFORATED DUODENAL ULCER

Duodenal and gastric ulcer diseases are jointly referred to as peptic ulcer disease. Although the pathophysiology and treatments are similar, duodenal ulcer disease warrants a brief independent discussion. Duodenal ulcer disease is three times as common as gastric ulcer disease (300,000 patients yearly). Malignancy is far less commonly associated with duodenal ulceration. Typically, the presentation is similar to that of gastric ulceration. However, the symptoms of duodenal ulceration are often alleviated with consumption of food. As in gastric ulceration, a better understanding of the pathophysiology has led to a decrease in operative indications. However, the operative indications/interventions are

similar. Evaluation utilizes endoscopy as the diagnostic standard.

As with gastric ulceration, treatment options may include medical, endoscopic, and surgical approaches. Surgical options are based on the same operative indications (bleeding, perforation, obstruction, and intractability). In the case of perforation, a duodenal ulcer is oversewn and a well-vascularized Graham patch is used to cover the defect. Highly selective vagotomy is preferred, but truncal vagotomy and drainage procedures are within the standard of care. Duration of symptoms, previous treatments, medication usage (NSAIDs), and comorbidity assist in operative planning. Postgastrectomy syndromes are, again, a well-documented complication.

## PERFORATED APPENDICITIS

Appendicitis is the most common emergent surgical procedure performed in Western countries. Reginald Herber Fitz, a Harvard Medical School pathologist, first described the pathologic process in 1889. He illustrated an event sequence of luminal obstruction, inflammation, perforation, abscess formation, and peritonitis. Presentation involves acute or gradual onset of midline pain (usually periumbilical, but occasionally epigastric) that begins as dull cramping (visceral pain). As the inflammatory process progresses, sharp stabbing pain is localized in the right lower quadrant (somatic pain). This is often associated with nausea, anorexia, and vomiting. In the predominant number of cases, fever will be absent.

Evaluation begins with a physical examination, laboratory studies, and plain films of the chest and abdomen. On examination, peritoneal signs (rebound/guarding) and pain with any movement (Dunphy's sign), with internal rotation of the hip (obturator sign), during extension of the hip (ileopsoas sign), and initiating in the right lower quadrant during palpation of the left lower quadrant (Rosving's sign) support the diagnosis without confirmation. Laboratory studies are often unremarkable. Leukocytosis of greater than 10,000/μl is seen in approximately two-thirds of patients. In cases in which the leukocytosis exceeds 20,000/μl, suspicion for perforation greatly increases. Hematuria, proteinuria, and pyuria are commonly encountered in the absence of urologic disease. Fecaliths and free intraperitoneal air are occasionally seen on plain films. Ultrasound findings of a target lesion or a thickened incompressible appendiceal wall can be 80% sensitive and 90% specific. Computed tomography is increasingly used in establishing diagnosis. With improvement in technology, computed tomography is often more accurate than ultrasound, and more capable of identifying an abnormally positioned appendix. Additionally, a negative study rules out a variety of abdominal pathologies and diminishes the need for costly hospitalization/observation. Barium contrast studies are safe and available, but are infrequently implemented in the presence of ultrasound or computed tomography.

In general, patients who present with a clinical picture suggesting appendicitis require exploration. This can be performed laparoscopically or via laparotomy. Laparoscopic appendectomy is diagnostic and therapeutic, often resulting in a reduction of postoperative pain and length of hospitalization when compared with laparotomy. Unfortunately, laparoscopy is associated with increased operative time (expense) and postoperative emesis. However, it is often beneficial in female patients when there exists complicated differentiation from gynecologic pathology. Appendectomy via laparotomy utilizing a muscle-splitting incision remains the standard of care. In cases of perforation, the fascia is closed while the skin and subcutaneous tissues are left to close by secondary intention.

The factor associated with the greatest morbidity and mortality in cases of appendicitis is delay in diagnosis and treatment. Approximately 64% of patients present with a retrocecal appendix, which can delay the diagnosis. Diagnostic delay results in increased rates of perforation. Perforation is associated with less than 5% mortality, compared to 0.6% in nonperforated appendicitis. The perforation rate is approximately 4% in young patients and is greatly increased in the elderly. A negative appendectomy rate of approximately 25% is considered acceptable when compared with the complications associated with delay in treatment.

## PERFORATED DIVERTICULITIS

The word "diverticulum" is derived from the Latin *deverticulum*, a "by-road" or "diversion" (French, *de-verto*; "to turn aside"). The diverticula arise as the colonic mucosal tissue herniates through the muscularis. Generally, two types of diverticula are seen. Right colon diverticula are usually congenital and are more commonly seen in Asian countries. Conversely, sigmoid diverticula usually occur as a consequence of a low-fiber diet (high intraluminal pressures) and are more prevalent in Western societies. Diverticulitis was initially described in the early twentieth century and has significantly increased in prevalence. It is incidentally noted in one-third of the population over 45 years of age (two-thirds over 85 years).

Diverticulitis typically presents with acute or subacute onset of left lower quadrant abdominal pain,

constipation, diarrhea, fever, and, infrequently, a palpable mass. The expression "left-sided appendicitis" has described this clinical presentation. The diagnosis is largely based on clinical findings and can be made in the absence of further imaging. However, computed tomography (CT) with intravenous contrast has been used as the initial diagnostic exam to provide objective data, assist in treatment planning, and elucidate difficult clinical scenarios. Characteristic findings on CT include thickening of the colonic wall, pericolonic fat infiltration, and pericolonic/distant abscess formation. The role of endoscopy and barium enema is limited during the acute episode due to the risk of perforation.

Diverticular disease can be categorized in two groups, asymptomatic diverticulosis and acute uncomplicated or complicated diverticulitis. Asymptomatic diverticular disease is found incidentally and can benefit from a high-fiber diet. No additional treatment may be required. Acute uncomplicated diverticulitis presents with left lower quadrant pain, fever, and leukocytosis (occasionally constipation/diarrhea, nausea/vomiting, and dysuria). It is defined as local perforation without abscess, bleeding, or free perforation. Therapy includes a high-fiber diet and broad-spectrum antibiotics. Coverage for gram-negative and anaerobic bacteria is implemented. Stable patients without diffuse abdominal findings on examination can be treated as outpatients, with close followup as judged by an experienced surgeon. In the event that these patients worsen clinically (pain/fever), admission and further evaluation/intervention are required. If no findings are noted on CT, but clinical improvement does not occur within 72–96 hours, surgical intervention can be considered. For immunocompromised patients or those unable to tolerate oral medications, admission for administration of intravenous antibiotics is preferred.

The presence of an abscess, fistula, intestinal obstruction, or free perforation classifies diverticulitis as complicated (complicated diverticulitis). The incidence of free perforation is rare, but the mortality can be as high as one-third. Traditional practice has been to resect with the initial episode. However, more conservative methods have emerged with great success. Small pericolic abscesses can be managed conservatively, whereas larger and more distant fluid collections can be successfully drained under CT guidance. In cases when drainage is inadequate, urgent surgery is required. Surgical treatment generally includes resection of the diseased sigmoid, proximal diversion, and the creation of a Hartman's pouch. Primary bowel anastomosis can be considered only under the best possible conditions and in experienced hands. Recent advent of laparoscopic resection has offered a reduction in pain and hospitalization when performed under elective circumstances.

## See Also the Following Articles

**Appendicitis • Diverticulosis • Duodenal Ulcer • Endoscopy, Complications of • Gastric Ulcer**

## Further Reading

Author Unknown. (1995). *In* "Steadman's Medical Dictionary," 26th Ed., pp. 477, 513, 1325. Williams & Wilkins, Philadelphia.

Cameron, J. L. (2001). *In* "Current Surgical Therapy," 7th Ed., pp. 7–12, 77–81, 267–272. Mosby, Philadelphia.

Greenfield, L. J., *et al.* (1997). *In* "Surgery: Scientific Principles and Practice," 2nd Ed., pp. 1246–1261. Lippincott-Raven, Philadelphia.

Greenfield, L. J., *et al.* (2001). *In* "Surgery: Scientific Principles and Practice," 3rd Ed., pp. 750–766, 1224–1235. Lippincott Williams & Wilkins, Philadelphia.

Lawrence, P. F. (1988). *In* "Essentials of General Surgery," pp. 187–200. Williams & Wilkins, Baltimore.

Sabiston, D. C. (1991). *In* "Textbook of Surgery: The Biologic Basis of Modern Surgical Practice," 14th Ed., pp. 736–755. W. B. Saunders, Philadelphia.

Sabiston, D. C. (1997). *In* "Textbook of Surgery: The Biologic Basis of Modern Surgical Practice," 15th Ed., pp. 825–846, 964–970. W. B. Saunders, Philadelphia.

Silen, W. (2000). *In* "Copes Early Diagnosis of the Abdomen," pp. 83–103, 105–119, 268–286. Oxford University Press, Cambridge.

# Peristalsis

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**monosynaptic spinal reflex** Neural reflex circuit in the spinal cord consisting of a sensory neuron and a motor neuron with a single synaptic connection between the two.

**reflexes** Motor responses to sensory stimulation; each time a "hardwired" neural circuit is activated, the responses are repeated in the same way.

**Peristalsis is a term used in reference to the organized propulsion of material over variable distances within the lumen of the esophagus, the small and large intestine, and sometimes the distal stomach. The muscle layers of the intestine and esophagus behave in a stereotypical pattern to achieve peristaltic propulsion. Integrated neural circuits of the enteric nervous system control the behavior of the intestinal musculature. Peristaltic propulsion in the esophagus is controlled by signals transmitted from the brain stem to the esophagus by the vagus nerves and by the enteric nervous system.**

## PERISTALTIC PROPULSION

During peristalsis (Fig. 1), the longitudinally oriented muscle in the segment ahead of the advancing intraluminal contents contracts while the circumferentially oriented muscle layer relaxes in the same segment. The esophagus and intestine are tubes that behave physically like a cylinder with constant surface area. Shortening of the longitudinal axis of the cylinder is accompanied by widening of the cross-sectional diameter. Simultaneous shortening of the longitudinal axis and relaxation of the circular muscle result in expansion of the lumen. This prepares a receiving segment for the forward-moving intraluminal contents during peristalsis.

The second component of stereotypic peristaltic behavior is contraction of the circumferentially oriented muscle layer in the segment behind the advancing intraluminal contents. The longitudinally oriented muscle layer in this segment relaxes simultaneously with contraction of the circular muscle, resulting in conversion of this region to a propulsive segment that propels the luminal contents ahead, into the receiving segment. Intestinal segments ahead of the advancing front become receiving segments and then propulsive segments in succession as the complex of propulsive and receiving segments travels along the intestine.

## PERISTALTIC REFLEX

Peristaltic reflex is a term sometimes applied inappropriately; it is not synonymous with the multiple patterns of coordinated propulsive motility that occur in the

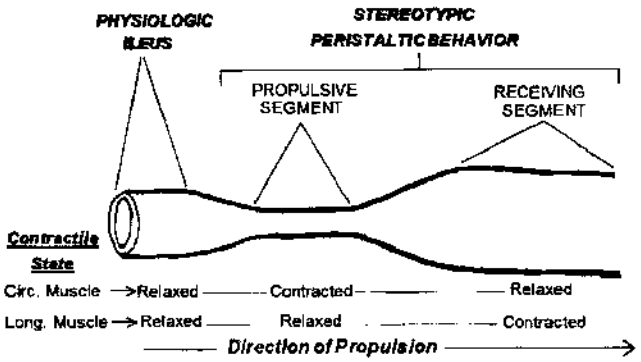


**FIGURE 1** The circumferential and longitudinal muscle layers of the intestines behave in a stereotypical pattern during peristaltic propulsion. A "hardwired" reflex circuit in the enteric nervous system determines the pattern of behavior of the two muscle layers. During peristaltic propulsion, the longitudinal muscle layer in the segment ahead of the advancing intraluminal contents contracts while the circumferential muscle layer relaxes simultaneously. Simultaneous shortening of the longitudinal intestinal axis and relaxation of the circumferential muscle in the same segment result in expansion of the lumen, which becomes a receiving segment for the forward-moving contents. The second component of the reflex is contraction of the circular muscle in the segment behind the advancing intraluminal contents. The longitudinal muscle layer in the same segment relaxes simultaneously with contraction of the circular muscle, which results in conversion of this region to a propulsive segment that propels the luminal contents ahead into the receiving segment. The reflex circuits are coupled in series along the intestine, such that receiving segments convert to propulsive segments as the next segment in line becomes a receiving segment. Propulsive segments then return to their previous state of physiologic ileus. The distance over which the peristaltic reflex circuit for the formation of propulsive and receiving segments is activated in sequence down the bowel determines the length of bowel over which propulsion occurs in one or the other of the intestinal motility patterns.

 

small and large intestine during different digestive states. The peristaltic reflex is, rather, the intestinal analogue of spinal motor reflexes, such as the monosynaptic patellar and Achilles tendon reflexes. Monosynaptic spinal reflexes are investigator-evoked artifacts arising from connections of stretch receptors in the muscle to alpha spinal motor neurons that innervate the same muscle. They reflect the effects of sudden activation of stretch receptors (i.e., muscle spindles) in the muscle and have little relevance for understanding the complexity of neural control of movement. The peristaltic reflex is much the same in that it is a fixed response evoked by investigational stretching of the intestinal wall or stroking of the mucosa. It is like a spinal reflex in that it is a motor response to sensory stimulation, and is repeated the same way each time the "hardwired" reflex circuit is activated. The peristaltic reflex circuit is "wired" such that it evokes relaxation of the circumferentially oriented muscle layer and contraction of the longitudinal muscle below the point of stimulation, and contraction of the circumferentially oriented muscle layer above the point of stimulation.

Like the spinal reflexes, the peristaltic reflex is positioned at the lowest level of the hierarchical organization of neural control of intestinal motility, and undoubtedly underlies each of the various patterns of propulsive motility that impart functionality to the intestine during daily life. As with a spinal motor reflex, the sequencing of the pattern of behavior of the various muscle groups is hardwired into the circuitry, whereas the repetition rate of the pattern and strength of each motor component of the pattern are adjusted by sensory feedback or other commands to compensate automatically for local loads and higher functional demands on the intestine as a whole. Added factors requiring a higher order of neural control are the distance and direction in which propulsion occurs for the patterns of motility that characterize the various digestive states. Short-distance propulsion in the postprandial digestive state, propulsion over intermediate distances during interdigestive motility (i.e., migrating motor complex), long-distance power propulsion all in the orthograde direction, and retropulsion during emesis are neural control requirements unique to the enteric nervous system. Better understanding of the neural basis for intestinal motility will require moving forward from the overworked concept of the peristaltic reflex and on to investigation of microcircuits in positions at levels of organization beyond the reflex hardwiring that faithfully reproduces the muscle behavior each time the investigator stretches the intestinal wall or strokes the mucosa.

## See Also the Following Articles

**Emesis • Enteric Nervous System • Migrating Motor Complex • Postprandial Motility • Power Propulsion**

## Further Reading

Kosterlitz, H. (1967). Intrinsic intestinal reflexes. *Am. J. Dig. Dis.* 12, 245–254.

Kosterlitz, H., and Robinson, J. (1959). Reflex contractions of the longitudinal muscle coat of the isolated guinea-pig ileum. *J. Physiol. (Lond.)* 146, 369–379.

Sifrim, D., Janssens, J., and Vantrappen, G. (1992). A wave of inhibition precedes primary peristaltic contractions in the human esophagus. *Gastroenterology* 103, 876–882.

Wood, J. (1994). Physiology of the enteric nervous system. *In* "Physiology of the Gastrointestinal Tract" (L. Johnson, D. Alpers, J. Christensen, E. Jacobson, and J. Walsh, eds.), 3rd Ed., Vol. 1, pp. 423–482. Raven Press, New York.

Wood, J., Alpers, D., and Andrews, P. (1999). Fundamentals of neurogastroenterology. *Gut* 45, I–44.

# Peritoneal Disorders

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**peritonitis** Inflammation of the peritoneal linings of the abdominal cavity; may be of infectious, chemical, or unknown origin.

**peritoneal mesothelioma** A rare malignant tumor arising from the peritoneal lining of the abdominal cavity.

**pseudomyxoma peritonei** A rare condition manifested by diffuse, gelatinous implants of the peritoneal cavity and omentum arising from mucinous neoplasms of the ovary or appendix.

**Peritonitis, an inflammation of the peritoneal lining of the abdominal cavity, is the most common peritoneal disease and may be of infectious, chemical, or unknown origin. Other peritoneal disorders include peritoneal mesothelioma, a rare malignant tumor that arises from the peritoneal lining of the abdominal cavity, and pseudomyxoma peritonei, a rare condition manifested by diffuse, gelatinous implants of the peritoneal cavity and omentum that arises from mucinous neoplasms of the ovary or appendix.**

## PERITONITIS

The most common disorder of the peritoneum is inflammation, or peritonitis, which is usually of infectious origin. Peritonitis can be classified into two types based on etiology.

### Primary Peritonitis

Primary peritonitis occurs without an identifiable source of infection, usually in patients with preexisting ascites (most commonly cirrhosis in adults or nephrotic syndrome in children). Diagnosis is made by cell count and culture of the ascitic fluid. Treatment requires antibiotic coverage appropriate for both gram-positive and gram-negative bacteria, because *Escherichia coli* and *Klebsiella pneumoniae* are increasingly common in ascitic fluid cultures.

### Secondary Peritonitis

Secondary peritonitis, much more common than primary peritonitis, is caused by an intra-abdominal infection, such as perforation of the bowel, and can be further divided into acute suppurative, granulomatous, and aseptic (chemical) forms. Acute suppurative peritonitis is usually caused by spillage of intestinal contents into the peritoneal cavity as a result of primary intra-abdominal disease (e.g., perforated peptic ulcer, appendicitis, diverticulitis, perforated carcinoma), penetrating trauma, or iatrogenic perforation after instrumentation or radiologic procedures. Early signs of peritoneal inflammation include nausea, vomiting, anorexia, and vague poorly localized abdominal pain. As the infection progresses, these symptoms may worsen and the pain becomes more focal as the inflammation of the visceral peritoneum extends to the parietal peritoneal. Fever and signs of hypovolemia (tachycardia, dry mucous membranes, low urinary output) may also be present. Treatment consists of proper fluid resuscitation, antibiotic therapy, and prompt treatment of the underlying pathology usually through surgical intervention.

Granulomatous peritonitis may be from fungal, amebic, or parasitic sources, but tubercular infection is by far the most common etiology. There has been an unfortunate resurgence of tuberculous peritonitis (Fig. 1) due to an increase in the prevalence of acquired immune deficiency syndrome, although it still

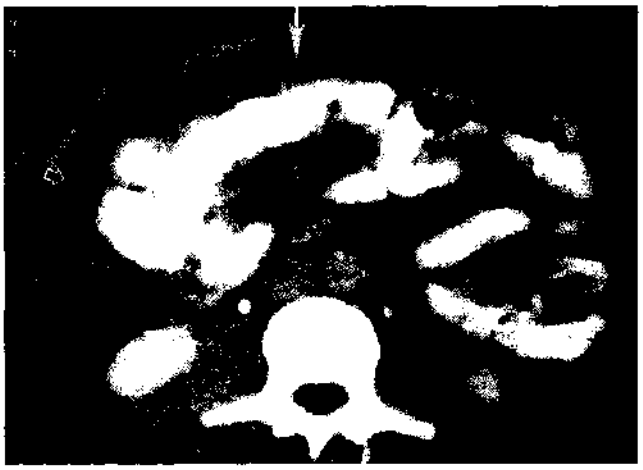

FIGURE 1 Computed tomography scan demonstrates ascites (open arrow) and small bowel thickening (filled arrow) in a patient with tuberculous peritonitis. Courtesy of Charles J. Fagan, M.D. (Galveston, TX).

 

complicates less than 1% of all *Mycobacterium tuberculosis* infections. The infection usually originates outside the peritoneum from diseased bowel, from salpingitis, or through hematogenous spread of a primary pulmonary infection. Unlike suppurative peritonitis, onset of symptoms is quite insidious with 70% of patients displaying fever, malaise, anorexia, weakness, or weight loss for more than 4 months prior to diagnosis. Ascites and diffuse tenderness are usually present and should suggest the illness in high-risk or immunocompromised patients with unexplained fever and malaise. The disease usually responds rapidly to anti-tuberculosis therapy with the exception of cases involving newly emergent drug-resistant mycobacteria.

Chemical (aseptic) peritonitis results from spillage of irritant materials that are initially sterile, but with time become secondarily infected and present as suppurative peritonitis. Bile, urine, and chyle are potential endogenous causes, whereas iatrogenic etiologies include barium from radiologic studies (with a concurrent perforation) and starch powder from surgical gloves. Patients who undergo continuous ambulatory peritoneal dialysis may acquire infections of the normally sterile catheter and peritoneum, leading to bacterial peritonitis. Treatment is similar to suppurative peritonitis—fluid resuscitation, appropriate antibiotic coverage, and surgery to control the source of peritoneal contamination.

## PRIMARY MESOTHELIOMA

Similar to pleural forms, primary peritoneal mesothelioma is linked to asbestos exposure, although only 20–40% of mesotheliomas occur in the peritoneum (Fig. 2). Clinical presentation includes nonspecific abdominal pain, nausea, vomiting, weight loss, and diarrhea; ascites is found in 90% of patients. Most cases are not identified until laparoscopy or laparotomy is performed. Curative treatment is rare because the disease is usually quite advanced at the time of diagnosis. Surgery serves only to confirm the diagnosis and provide palliative procedures to relieve obstruction. Chemotherapy and radiotherapy have shown minimal success although newer intraperitoneal chemotherapy and immunotherapy may improve the prognosis.

## PSEUDOMYXOMA PERITONEI

Pseudomyxoma peritonei is a rare condition manifested by diffuse, gelatinous implants of the peritoneal cavity and omentum arising from mucinous neoplasms of the ovary or appendix (Fig. 3). Most cases occur in women

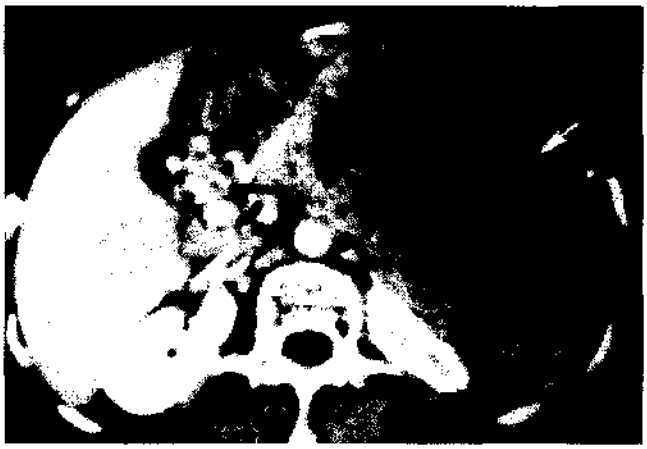

FIGURE 2 Computed tomography scan demonstrates diffuse mesenteric and peritoneal involvement of a soft tissue mass (arrow) causing displacement of intra-abdominal organs in a patient with peritoneal mesothelioma. Courtesy of Charles J. Fagan, M.D. (Galveston, TX).

who have disease in both organs; thus, the tissue of origin is not established. Patients may present with abdominal pain or increasing girth due to mucinous ascites, but most diagnoses are made following surgical exploration for appendicitis or ovarian tumors. Computed tomography may reveal characteristic "scalloping" of the hepatic and bowel margins. Treatment is primarily surgical, to include aggressive debulking, appendectomy, bilateral oophorectomy, and omentectomy. Recurrence rates are high (approximately 75% of patients); however, due to the low grade of this malignancy, repeat debulking procedures are indicated and may improve outcome. Chemotherapy

FIGURE 3 Computed tomography scan demonstrates large gelatinous masses (arrows) in a patient with pseudomyxoma peritonei. Courtesy of Charles J. Fagan, M.D. (Galveston, TX).

may produce a modest survival advantage over surgery alone; radiotherapy appears to have no role in the treatment of pseudomyxoma peritonei.

### See Also the Following Articles

Ascites • Peritoneum, Anatomy and Development

### Further Reading

Bosscha, K., van Vroonhoven, T. J., and van der Werken, C. (1999). Surgical management of severe secondary peritonitis. *Br. J. Surg.* 86, 1371–1377.

Marshall, J. B. (1993). Tuberculosis of the gastrointestinal tract and peritoneum. *Am. J. Gastroenterol.* 88, 989–999.

Piazza, D., Caruso, F., Scaringi, S., Ferrara, M., Latteri, F., and Dell'Erba, D. (2000). Primary diffuse malignant peritoneal mesothelioma: Case report and update of therapy. *J. Surg. Oncol.* 75, 55–58.

Rimola, A., Garcia-Tsao, G., Navasa, M., Piddock, L. J., Planas, R., Bernard, B., and Inadomi, J. M. (2000). Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: A consensus document. *J. Hepatol.* 32, 142–153.

Sugarbaker, P. H., Shmookler, B., Ronnett, B. M., Chang, D., and Ambrose, N. S. (1999). Pseudomyxoma peritonei. *Br. J. Surg.* 86, 842.

# Peritoneum, Anatomy and Development

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**coelom** Body cavity of the embryo.
**mesothelium** Layer of flat cells derived from the mesoderm that lines the coelom.
**peritoneum** Serous membrane lining the abdominopelvic walls and investing the viscera.

**The peritoneum is the mesothelial lining of the peritoneal cavity and its contained viscera; it functions as a bidirectional dialysis membrane and thus plays a major role in defending against inflammatory processes of the abdomen. The peritoneum is the key organ involved in sensation of abdominal pain and is thus integral to diagnosing abdominal pathology.**

## EMBRYOLOGY AND DEVELOPMENT

The peritoneum and other body cavities begin to develop from the intraembryonic coelom near the end of the third week of gestation. The coelom has a parietal wall and a visceral wall, both lined by mesothelium; the parietal mesothelium is derived from somatic mesoderm whereas the visceral mesothelium is derived from splanchnic mesoderm. By the fourth week of gestation, the coelom appears as a horseshoe-shaped cavity in the cardiogenic and lateral mesoderm. The curve of the "horseshoe" represents the future pericardial cavity, and the lateral and caudal extensions represent the eventual pleural and peritoneal cavities (Fig. 1). These lateral areas communicate with the extraembryonic coelom. The development of the midgut involves a herniation through this communication into the umbilical cord, where the midgut develops into the small intestine and part of the large intestine. At this point, the intraembryonic coelom is divided into right and left halves that are divided by the ventral and dorsal mesenteries.

Toward the end of the fourth week of gestation, the lateral parts of the intraembryonic coelom move onto the ventral aspect of the embryo and the ventral mesentery degenerates, creating a large peritoneal cavity with a dorsal mesentery (Fig. 2). Until the seventh week of gestation, this peritoneal cavity communicates with the pericardial and pleural cavities through pericardioperitoneal canals; during the fifth and sixth weeks of gestation, folds form near the cranial and caudal ends of these canals. Fusion of these membranous folds with mesoderm ventral to the esophagus separates the pericardial and pleural cavities while fusion of the caudal pleuroperitoneal membranes forms the diaphragm and separates the pleural and peritoneal cavities. The peritoneal cavity then loses its connection with the extraembryonic coelom during the tenth week of gestation, when the intestines return to the abdomen from the

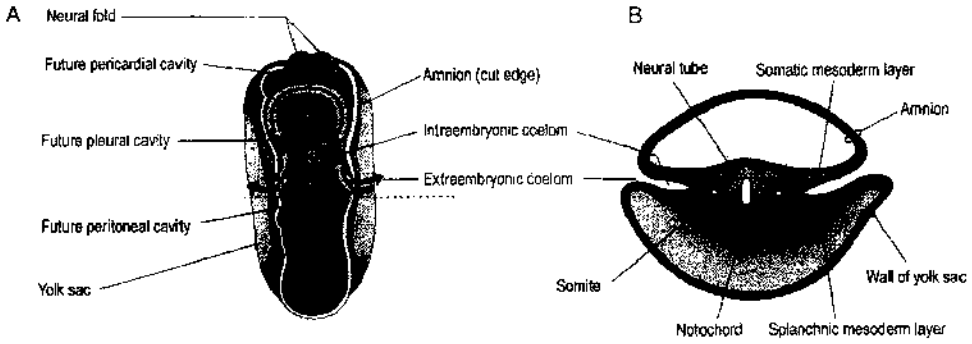


FIGURE 1 (A) Drawing of a dorsal view of a 22-day-old embryo, showing outline of the horseshoe-shaped intraembryonic coelom. (B) Transverse section through embryo at the level shown in A. Reproduced with permission from Moore and Persaud (1998).

umbilical cord. At this point, the peritoneum lines the abdominal wall and invests the abdominal viscera.

## ANATOMY AND PHYSIOLOGY

The peritoneum is made up of the visceral and parietal layers; it has a total surface area of approximately 2 $m^2$. The visceral peritoneum covers the intraperitoneal organs and forms the mesenteries by which they are suspended. The peritoneum and its mesentery are supplied mainly by the splanchnic blood vessels, and, to a lesser extent, by branches of the visceral and parietal peritoneum.

Differences arise in the innervations of the visceral and parietal peritoneum, leading to differing patterns of sensation of painful stimuli. The visceral peritoneum receives its innervation from the autonomic nervous system and responds primarily to traction and pressure or distension; painful stimuli are perceived as a poorly localized, dull pain. In general, pain in the epigastric region is referred from a foregut structure (e.g., stomach, duodenum, pancreas, or biliary tract); pain in the periumbilical area is the result of stimulus to a midgut structure (appendix, jejunum, or ileum) and pain in the hypogastric or suprapubic region is from a hindgut source (distal colon or rectum). In contrast, both somatic and visceral afferent nerves innervate the parietal peritoneum. Therefore, noxious stimuli are perceived as a localized, sharp pain with rebound tenderness and are referred to as "peritonitis."

Functionally, the peritoneum serves as a bidirectional dialysis membrane through which both large- and small-molecular-weight solutes pass by simple passive diffusion. Absorption can be altered by changes in intraabdominal pressure, temperature, pH, and portal pressure in addition to lymphatic blockade and peritoneal scarring. The peritoneum contains a complex defense system that protects against inflammatory processes. This system consists mainly of mechanical clearance of the peritoneal cavity, the bactericidal

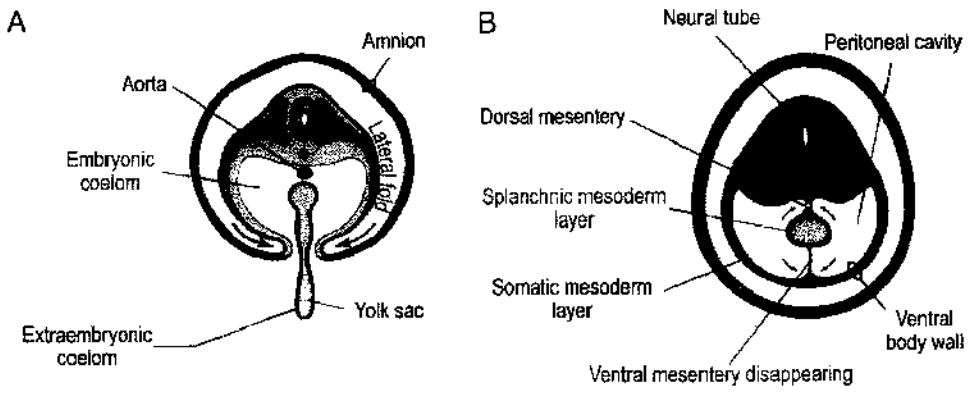


FIGURE 2 (A) Transverse section illustrating embryonic folding and its effects on the intraembryonic coelom and other structures. (B) Transverse section illustrating formation of the ventral body wall and disappearance of the ventral mesentery. Arrows indicate the junction of the somatic and splanchnic mesoderm. Reproduced with permission from Moore and Persaud (1998).

mechanisms of polymorphonuclear leukocytes, and sequestration mechanisms such as fibrin trapping of bacterial activation of complement. The peritoneum is the key organ in sensation of abdominal pain and in the physical diagnosis of ongoing intraabdominal pathology.

## See Also the Following Articles

**Development, Overview • Gastrointestinal Tract Anatomy, Overview • Peritoneal Disorders**

## Further Reading

Aune, S. (1970). The effect of transperitoneal fluid transport on the transfer of solutes. *Scan. J. Gastroenterol.* 5, 241–252.

Berndt, W. O., and Gosselin, R. E. (1962). Differential changes in permeability of mesentery to rubidium and phosphate. *Am. J. Physiol.* 202, 761–767.

Heel, K. A., and Hall, J. C. (1996). Peritoneal defenses and peritoneum-associated lymphoid tissue. *Br. J. Surg.* 83, 1031–1036.

Moore, K. L., and Persaud, T. V. N. (1998). "The Developing Human," 6th Ed. W. B. Saunders, Philadelphia.

Shear, L., Castellot, J. J., Shinaberger, J. H., Poole, L., and Barry, K. G. (1966). Enhancement of peritoneal fluid absorption by dehydration, mercaptomerin and vasopressin. *J. Pharmacol. Exp. Ther.* 154, 289–297.

Shear, L., Swartz, C., Shinaberger, J. A., and Barry, K. G. (1965). Kinetics of peritoneal fluid absorption in adult man. *N. Engl. J. Med.* 272, 123–127.

Topley, N., and Williams, J. D. (1994). Role of the peritoneal membrane in the control of inflammation in the peritoneal cavity. *Kidney Int. Suppl.* 48, S71–S78.

# Pernicious Anemia

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**intrinsic factor** A glycoprotein that binds cobalamin specifically, attaches to a receptor (cubilin) on the apical membrane of the ileal epithelial cell, and is internalized together with its cobalamin by that cell.

**Pernicious anemia (PA) is defined as cobalamin (vitamin $B_{12}$) deficiency caused by that vitamin's malabsorption because of the patient's failure to secrete gastric intrinsic factor. This anachronistic hematological name for what is really a gastroenterological disorder was coined originally to reflect the megaloblastic anemia that cobalamin deficiency often causes. However, many patients diagnosed with PA have little or no anemia; moreover, folate deficiency and rare metabolic disorders can cause the same anemia. PA does not refer to cobalamin deficiency produced by any other mechanisms, such as intestinal disease.**

## PATHOGENESIS AND DIAGNOSIS

The parietal cell synthesizes intrinsic factor (IF) and secretes it, as well as acid, into the gastric lumen. The pathogenetic basis of pernicious anemia (PA) is the inability of the parietal cell to do so. Without IF, cobalamin cannot be absorbed efficiently.

In the more common, acquired form of PA, the lack of IF results from severe atrophic gastritis with loss of parietal cells. The gastritis tends to involve the fundus while sparing the antrum and the disorder has many features of an autoimmune process. Antibody directed at the $H^+,K^+$-ATPase pump of the parietal cell circulates in the blood in 70–90% of patients, but it is characteristic for atrophic gastritis in general and is not specific for PA. Approximately 60–70% of patients with PA have circulating antibodies to IF, whose presence is virtually diagnostic for pernicious anemia. Serum gastrin levels are elevated in >80% of cases and often massively so. The gastritis in approximately 10% of patients with acquired PA is diffuse, does not spare the antrum, and is accompanied by fewer immune phenomena. A much rarer form of PA is an unrelated inborn error of IF synthesis in which the stomach and parietal cell function are otherwise normal.

Whereas atrophic gastritis itself is quite common, PA is relatively uncommon. Although PA predominates in the elderly, approximately 2% of whom have unsuspected PA, it affects younger individuals too, especially among black women.

The diagnosis of PA is usually established by proving IF absence directly by assay of gastric juice or indirectly by showing abnormal absorption of radioactive cobalamin with correction when IF is given exogenously (Schilling test). A presumptive diagnosis can also be made by demonstrating antibody to IF in the blood.

## DEFICIENCY OF COBALAMIN

When IF secretion fails, cobalamin absorption virtually ceases and a negative cobalamin balance gradually develops. The progression is slow because the daily turnover of cobalamin is only approximately 0.1% of the body stores. Several years usually elapse before the clinical signs of cobalamin deficiency begin to appear. Although all cells require cobalamin, the most common manifestations of cobalamin deficiency, whether due to PA or other diseases, are hematological and neurological ones. Patients can have both or just one of these two types of manifestations—or, if caught early, neither one of them.

Megaloblastic anemia is characterized by large red blood cells (a high mean corpuscular volume is often the earliest expression of cobalamin deficiency), abnormal nuclei, and eventually pancytopenia as ineffective hematopoiesis progresses. The "methylfolate trap" produced by cobalamin deficiency causes the impaired DNA synthesis of this anemia, which is indistinguishable from that in folate deficiency. The neurological problems typically involve the posterior, and occasionally lateral, columns of the spinal cord and peripheral nerves. However, all parts of the nervous system can be affected, including cerebral function. The biochemical basis for the neurological dysfunction is unknown.

## COMPLICATIONS

Two types of disorders complicate PA more often than expected. One is organ-specific immune disorders such as endocrinopathy, especially hypothyroidism, which can affect 5% of patients. The other complication is gastric neoplasia. The risk of gastric carcinoma is increased several-fold in PA and gastric carcinoids may be even more common than cancer.

## THERAPY AND MANAGEMENT

The cobalamin deficiency is easily treated: megaloblastic anemia is readily reversed and, if cobalamin therapy is begun early enough, so are the neurologic abnormalities. However, the gastric defect persists, making lifelong cobalamin replacement mandatory. Because cobalamin is absorbed poorly in PA, treatment is usually by injection (oral cobalamin can be used, but very large daily doses must be given). Most experts advise endoscopy for neoplasia in every patient at the time of diagnosis and thyroid function should be monitored periodically.

### See Also the Following Articles

**Cobalamin Deficiency • Gastrin • Intrinsic Factor • Parietal Cells • Vitamin B12: Absorption, Metabolism, and Deficiency**

### Further Reading

Carmel, R. (1996). Prevalence of undiagnosed pernicious anemia in the elderly. *Arch. Intern. Med.* 156, 1097–1100.

Carmel, R., and Rosenblatt, D. S. (2003). Disorders of cobalamin and folic acid metabolism. *In* "Blood: Principles and Practice of Hematology" (R. I. Handin, S. E. Lux, and T. P. Stossel, eds.), 2nd Ed., pp. 1361–1397. Lippincott Williams & Wilkins, New York, in press.

Chanarin, I. (1979). "The Megaloblastic Anaemias," 2nd Ed. Blackwell Scientific, Oxford, UK.

Kokkola, A., Sjöblom, S.-M., Haapiainen, R., Sipponen, P., Puolakkainen, P., and Järvinen, H. (1998). The risk of gastric carcinoma and carcinoid tumours in patients with pernicious anaemia: A prospective follow-up study. *Scand. J. Gastroenterol.* 33, 88–92.

Nicolas, J.-P., and Guéant, J.-L. (1995). Gastric intrinsic factor and its receptor. *Bailliere Clin. Hematol.* 8, 515–531.

Toh, B.-H., van Driel, I. R., and Gleeson, P. A. (1997). Pernicious anemia. *N. Engl. J. Med.* 337, 1441–1448.

# Pharmacology, Overview

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**agonist** Drug or substance that binds to a receptor on a cell to induce a response.

**antagonist** Drug or substance that binds to a receptor on a cell to prevent or reverse the response of an agonist.

**inflammatory bowel disease** A severe inflammatory disorder of the gastrointestinal tract characterized by abdominal pain, rectal bleeding, diarrhea, fever, and severe weight loss.

**irritable bowel syndrome** A functional disorder of the gastrointestinal (GI) tract characterized by abdominal pain and discomfort associated with altered bowel habits, occurring in the absence of structural or biochemical abnormalities within the GI tract.

**neurotransmitter** A chemical released by neurons in the brain or peripheral nervous system to communicate with other neurons.

**peptic ulcer disease** A disorder of the upper gastrointestinal tract (esophagus, stomach, and duodenum), characterized by inflammation and ulceration.

**prebiotic** Agents that stimulate selectively the growth of bifidobacteria and lactobacilli in the gut.

**probiotic** A live microbial food supplement that affects the host by improving its intestinal microbial balance.

**prokinetics** Agents that stimulate the movement of lumenal contents along the gastrointestinal tract.

**receptor** A protein structure to which neurotransmitters, hormones, and pharmaceutical bind selectively to produce a functional effect.

**Disorders of the gastrointestinal (GI) tract are common, unpleasant, and complex, affecting the mucosa, musculature, and innervation from the esophagus to the colon. These disorders are manifested as ulceration, inflammation, obstruction, diarrhea, constipation, and abdominal pain. Over the past few years, although the pharmacological treatment of many GI disorders has improved significantly, the management of GI disorders still continues to pose a significant challenge to clinicians. However, as understanding of the biology of GI disorders expands, the potential for the future development of novel pharmacological agents increases. This article provides a brief pharmacological overview of the approaches to treat a series of important GI disorders.**

## PEPTIC ULCER AND GASTROESOPHAGEAL REFLUX DISEASE THERAPY

Under physiological conditions, cytoprotective mechanisms exist to prevent intraluminal contents from damaging the mucosal lining of the gastrointestinal (GI) tract. However, under pathophysiological conditions, there is an imbalance between defensive factors, on the one hand, and offensive factors, on the other, leading to mucosal inflammation and injury. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the mainstay for the treatment of musculoskeletal inflammatory diseases, yet they represent one of the major causes of serious GI injury. Traditional NSAIDs are nonselective inhibitors of cyclooxygenase (COX) isoforms COX-1 and COX-2 and destroy the mucosal defense system in part through decreasing the synthesis of cytoprotective COX-1-derived anti-inflammatory prostaglandins in the upper GI tract. GI toxicity associated with NSAIDs includes dyspepsia, gastroduodenal ulcers, and severe gastric bleeding. Newer NSAIDs that act selectively to inhibit COX-2-derived pro-inflammatory prostaglandins, but not COX-1, have significantly reduced GI toxicity. Another major cause of peptic ulcer disease is *Helicobacter pylori* infection. Gastric damage also occurs in critically ill patients due to stress-related mucosal disease, thought to be caused by decreased blood flow, mucosal ischemia, and hypoperfusion–reperfusion injury.

The goals of treatment for peptic ulcer disease include relieving symptoms, increasing healing rate, preventing complications such as bleeding, perforations, and obstruction, and finally, avoiding recurrence. Pharmacological treatment for peptic ulcer disease includes the use of over-the-counter (OTC) antacids to neutralize the pH of gastric contents. Subsequently, histamine type 2 ($H_2$)-receptor antagonists, such as cimetidine (Tagamet), ranitidine (Zantac), nizatidine (Axid), and famotidine (Pepcid), are used to inhibit acid secretion. Proton pump inhibitors, which include omeprazole (Prilosec), lansoperazole (Prevacid),

 

rabeprazole (Aciphex), pantoperazole (Protonix), and esomeprazole (Nexium), are able to effectively suppress basal and stimulated gastric acid secretion by noncompetitive inhibition of the $H^+$,$K^+$-ATPase pump on the parietal cell. Other agents that can be employed to treat peptic ulcer disease include coating agents, such as sucralfate (Carafate), an aluminum salt of a sulfated disaccaride that coats the mucosal lining and allows healing to occur. For those patients who present with NSAID-induced peptic ulcer disease, the use of the synthetic prostaglandin analogue misoprostil (Cytotec) in combination with the NSAID has reduced the incidence of peptic ulcer disease. For patients who test positive for *H. pylori* infection, eradication of the microorganism results in ulcer healing and reduces the risk of ulcer recurrence and complications. Eradication of *H. pylori* is complex, requiring a 10- to 14-day multidrug regimen of antibiotics and acid suppression. However, newer approaches to improve the eradication of *H. pylori* will likely improve patient compliance, be devoid of the potential for antimicrobial resistance, and have a lower cost.

Another common disorder of the upper GI tract is gastroesophageal reflux disease (GERD), which is defined as the excessive backflow of gastric contents into the esophagus. Symptoms of GERD include frequent or daily heartburn, which can progress to esophageal injury. Extraesophageal injury can also occur in association with GERD, resulting in hoarseness, vocal cord granulomas, dental erosions, chronic cough, bronchitis, asthma, and unexplained chest pain. Those at risk for GERD include infants younger than 12 months, though the condition is often self-limiting. Older adults are also at risk for GERD due to prolonged acid exposure over many years. Additional risk factors for GERD include increased acid secretion, use of drugs that reduce lower esophageal sphincter (LES) pressure, abnormalities in esophageal clearance mechanisms, gastroparesis (delayed gastric emptying), hiatal hernia, obesity, spinal cord injury, thyroid disease, Zollinger-Ellison syndrome, diabetes, and connective tissue disorders. The management of GERD requires a stepwise approach, and if lifestyle modifications fail to control symptoms, pharmacological therapy can be added. Drugs used for the management of GERD include OTC antacids to neutralize the pH of gastric contents. However, acid suppression remains the cornerstone of treatment for GERD since it provides adequate symptom relief, restores the quality of life, and prevents many of the potential complications associated with the disorder. H2-receptor antagonists are able to inhibit acid secretion, provide heartburn relief, and can be purchased OTC. Proton pump inhibitors suppress acid secretion and thus provide symptomatic relief for patients with GERD and represent the preferred therapy for the long-term management of patients with erosive esophagitis. Prokinetics (see next section) can be used in patients with GERD to increase LES pressure, promote gastric emptying, and enhance gastroduodenal coordination; however, the side effects of currently available agents often limit their usefulness.

## PROKINETIC AGENTS

Disorders such as gastroparesis, postoperative ileus, and pseudo-obstruction are recognized motility disorders that can affect propulsion and cause a delay in intestinal transit. Agents that accelerate GI transit are known as prokinetics and examples include cholinomimetics, such as bethanechol (Urecholine), which causes contraction of the GI musculature through stimulation of the cholinergic receptor ($M_2$) present on smooth muscle cells. However, the use of bethanechol is not popular since smooth muscle contractions induced by bethanechol are simultaneous rather than peristaltic. Additionally, cholinergic agonists have many side effects, including abdominal pain, diarrhea, salivation, and gastric acid secretion. Newer prokinetics came from a chemical class known as substituted benzamides, which include metoclopramide (Reglan), a dopamine $D_2$ receptor antagonist, and cisapride (Propulsid), which works through a serotonin receptor mechanism. Both agents enhance gastric emptying and increase intestinal transit through these different mechanisms. However, recent clinical experience has linked cisapride to life-threatening cardiac arrhythmias due to slowing of cardiac repolarization (QT prolongation), resulting in withdrawal of cisapride. This has created a gap in the prokinetic arena and appears to have resulted in the increased use of metoclopramide. Unfortunately, metoclopramide is associated with its own set of serious side effects, including gynecomastia, galactorrhea, fatigue, tremor or rigidity, and tardive dyskinesia. Motilides represent another class of prokinetic agents, so named because they stimulate the motilin receptor present on smooth muscle cells and enteric neurons. Examples include erythromycin, a macrolide antibiotic that can accelerate gastric emptying, enhance coordination between the stomach and duodenum, and stimulate the migrating motor complex. Although recent advances in the area of prokinetics have been limited, a new serotonin receptor agonist, tegaserod (Zelnorm), has been shown to stimulate intestinal transit and relieve the symptoms of constipation.

## PHARMACOLOGICAL TREATMENT OF INFLAMMATORY BOWEL DISEASE

Ulcerative colitis (UC) and Crohn's disease (CD), collectively known as inflammatory bowel diseases (IBDs), are immunoregulatory disorders of the GI tract, characterized by an abnormal, intense, and sustained inflammatory response to antigen stimulation. The current hypothesis is that hyperimmune reactivity toward the antigens of enteric bacteria, in a genetically susceptible host, is the basis for disease pathogenesis. Since IBD is characterized by spontaneous "flares" and remission, therapies are directed at treating the active inflammation and maintaining remission. 5-Aminosalicylates are the accepted therapy in the treatment of acute inflammation and maintaining remission in UC. Sulfasalazine (Azulfidine) was the first agent introduced for the treatment of UC and its pharmacologically active moiety is 5-aminosalicylic acid (5-ASA). Since 5-ASA is absorbed in the small intestine, delivery systems enabling 5-ASA to reach the colon before absorption occurs have been established. Specifically, such systems include enteric coatings that dissolve at the alkaline pH present in the terminal ileum or via a prodrug, such as balsalazide (Colozol), which is metabolized by bacterial azoreductases in the colon to release the therapeutically active moiety (5-ASA) and an inert carrier molecule. Topical therapy by enemas, suppositories, or foams has been an advance in the management of distal IBD. For severe active disease, glucocorticoids have clinical importance based on their immunosuppressive capacity against humoral and cell-mediated immune responses. Glucocorticosteroids bind to specific receptors that, on activation, translocate to the nucleus and either increase or decrease the expression of responsive genes. The effects of natural (cortisol) and synthetic [prednisolone (Prelone, Pedoapred, Orapred), dexamethasone (Decadron, Dexone, Hexadrol), budesonide] glucocorticoids involve regulation of the transcription and production of pro-inflammatory cytokines and tumor necrosis factor (TNF). A major limitation in the use of glucocorticoids for chronic treatment is that therapeutic doses are much greater than the daily glucocorticoid production and thus cause significant side effects. A partial solution to this problem is the development of topical-use glucocorticoids, which have low systemic bioavailability due to poor absorption or extensive local or first-pass hepatic metabolism. Topical instillation of budesonide, beclomethasone dipropionate, or prednisolone metasulfobenzoate into the colorectal area has been shown to be effective in patients with active distal IBD. New formulations of budesonide for controlled ileal release (EntocortEC) show high topical efficacy with minimal side effects in the treatment of mild to moderate, active CD. Immunosuppressive drugs with steroid-sparing properties may be beneficial in patients who failed to respond or who develop severe side effects to glucocorticoids. Cytotoxic agents, such as azathioprine (Imuran) and 6-mercaptopurine, have been found to be helpful in patients with CD. Cyclosporine, which suppresses cellular immunity, has been shown to be effective in patients with UC. Methotrexate, a folic acid antimetabolite that is structurally related to interleukin-1 (IL-1) and can interfere with its function, is currently used in patients with refractory IBD. However, the benefits of immunosuppressants are limited by the risk of high toxicity and serious side effects. Recent therapeutic strategies for the treatment of IBD are based on the ability of monoclonal antibodies to neutralize the effect of immune molecules. Infliximab (Remicade), a chimeric monoclonal immunoglobulin G1 antibody that neutralizes TNFα, has been found to have efficacy for refractory or fistulizing CD. Additionally, a therapy based on antibodies to CD4 is under investigation. Specific inhibitors of intercellular adhesion molecules have been designed to eliminate mucosal tissue damage by reducing leukocyte infiltration. Most recently, synthetic compounds (CNI-1493) or small protein molecules (granulocyte/macrophage colony-stimulating factor, bacterial/permeability-increasing protein $rBPI_{21}$) that are normally produced by the immune system have been manufactured by recombinant gene technology and are undergoing clinical trials. Recombinant anti-inflammatory cytokines IL-10 and IL-11, as well as peptide growth factors, are also in clinical development. Despite some promising results, the clinical significance of these new mediator-targeted strategies for IBD treatment is still limited by the inconvenience and high cost imposed by the intravenous or subcutaneous routes of drug administration. Future advances in the pharmacologic approach toward IBD and optimizing the clinical management of patients with IBD will lie in identifying factors predictive of response.

## TREATMENT OF DIARRHEA

Diarrhea, the frequent passage of watery/semiformed stool, is not only distressing but may be debilitating or even life-threatening. Acute uncomplicated diarrhea is often self-limiting; however, when diarrhea is chronic, it represents a major health problem and leads to significant dehydration and electrolyte imbalances. Diarrhea can be caused by infectious organisms or malabsorption and can also be drug-induced by agents such as tetracycline, specific antacids, antihypertensive

drugs such as reserpine or guanethidine, and chemotherapy. Diarrhea is also a prominent symptom of IBD. The management and pharmacological therapy of diarrhea depend on its severity. Acute uncomplicated diarrhea is often treated by OTC medications such as loperamide (Imodium), a peripherally acting opiate agent that decreases motility and limits epithelial secretion. Loperamide is efficacious and free of opiate-like and unwanted central nervous system side effects. In patients with chemotherapy-induced diarrhea, loperamide is moderately effective but for those patients refractory to loperamide, evidence suggests that octreotide, a somatostatin analogue, may be helpful in promoting intestinal absorption and relieving diarrhea. A common health problem among travelers to developing countries is diarrhea. The primary objective with pharmacotherapy for traveler's diarrhea is to reduce the symptoms and their duration with a combination of an antimicrobial agent and loperamide. Fluoroquinolones are the first drugs of choice for moderate to severe traveler's diarrhea; however, with the emergence of resistance, especially in *Campylobacter jejuni* ententis, other agents such as azithromycin and rifaximin are being investigated. For more severe forms of diarrhea, such as that seen with cholera infection, oral rehydration therapy can successfully treat the diarrhea. Future therapeutic approaches to prevent episodes of diarrhea may involve the use of prebiotics and probiotics to enhance the presence of bifidobacteria and lactobacilli in the gut to increase the body's natural defense against invading pathogens. However, future studies are needed to determine the efficacy and usefulness of these types of agents for the treatment of diarrhea.

## TREATMENT OF CONSTIPATION

Constipation is one of the most common medical complaints in Western countries and is defined as difficulty in passing or straining to pass stool, with less than three bowel movements per week. Constipation often results from disordered motility, leading to a delay in intestinal propulsion and slow transit. Other patients with constipation have a disorder in defecation with normal colonic transit; however, in the majority of cases, constipation results from a diet low in fiber. Constipation can also result from diabetes, pregnancy, and structural diseases of the colon and rectum. Constipation is a very common problem affecting the elderly and often results from polypharmacy since many drugs used by the elderly are known to be associated with constipation. Usually patients with constipation have mild to moderate symptoms and can be treated with increased fluid and fiber intake accompanied by regular exercise. Laxatives are commonly used to treat constipation and most are available OTC. Laxatives exert their effects by increasing stool frequency and stool weight. They are divided into (1) dietary fiber and bulk-forming laxatives, (2) saline and osmotic laxatives, and (3) stimulant laxatives. The dietary fiber and bulk-forming laxatives, such as bran, psyllium, and methylcellulose, increase the water content and mass of the stools, thereby stimulating intestinal peristalsis and decreasing colonic transit time. Saline and osmotic laxatives cause the retention of water within the GI tract because they are poorly absorbed. Examples include magnesium salts, which are charged and thus do not readily cross cell membranes and so remain in the lumen of the GI tract. Magnesium salts have a rapid onset of action and are used for cleansing the bowel prior to radiological procedures. Nonabsorbable sugars, such as lactulose, are also examples of osmotic laxatives, as are sorbitol, glycerin, and polyethylene glycol-based solutions. Stimulant laxatives, such as bisacodyl, senna, cascara, castor oil, and colace, increase colonic peristalsis and act as powerful cathartics. Taken together, however, there is a lack of published evidence for the long-term effectiveness of laxatives for the treatment of constipation. Probiotics have been suggested to improve motility and reduce fecal enzyme activity in patients with constipation. However, large carefully controlled clinical trials are needed to determine the usefulness of probiotic therapeutic approaches for relieving constipation.

## THERAPIES FOR IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome (IBS) is a disorder of the GI tract that often begins in early adult life and may affect up to 15–20% of the population; thus, it is associated with major health and economic effects. Currently, IBS is characterized according to symptoms of abdominal pain and discomfort associated with altered bowel function occurring in the absence of structural and biochemical abnormalities. The pathophysiology of IBS is due at least in part to heightened visceral sensitivity, altered intestinal motility, and psychosocial factors, which likely are mediated via alterations in the bidirectional cross talk between the neuronal networks in the brain (central nervous system) and the gut (enteric nervous system). Because functional bowel disorders are multifaceted, drug treatment of patients with IBS is complex; however, the management of IBS in North America was recently reviewed by the American College of Gastroenterology Functional Gastrointestinal Disorders Task Force and evidence-based recommendations were made.

Traditional IBS therapeutic approaches have included the use of antispasmodic agents, such as hyoscyamine and dicyclomine, which are thought to reduce high-amplitude contractions in the GI tract. Anticholinergic side effects, such as dry mouth, blurred vision, and constipation, limit their usefulness. Moreover, there are insufficient data from clinical trials to determine the effectiveness of antispasmodic agents in patients with IBS. Antidiarrheal agents, such as loperamide, have been shown to decrease stool frequency and improve stool consistency in IBS patients; however, there is no demonstrable effect of loperamide on the relief of abdominal pain and bloating. Laxatives, such as fiber, are effective at relieving constipation but there is no demonstrable effect of bulking agents on the relief of abdominal pain and bloating in IBS. There is a limited amount of data suggesting that antidepressant therapy may provide pain relief in IBS patients. However, tricylic antidepressants, such as amitriptyline, desipramine, trimipramine, and doxepin, have not been shown to be more effective than placebo in clinical trials. The effectiveness of serotonin reuptake inhibitors for the treatment of IBS has not been carefully documented, though preliminary evidence is promising.

Recent advances in the understanding of gut physiology have led to the introduction of two novel pharmacological approaches for the treatment of IBS, both targeted toward specific receptor systems, which are likely to improve the treatment of patients with IBS. The 5-hydroxytryptamine type 3 ($5\text{-}HT_3$) receptor antagonist alosetron (Lotronex) has been shown to reduce the symptoms of IBS in female patients with diarrhea. Alosetron has received Food and Drug Administration (FDA) approval for the treatment of women with severe diarrhea-predominant IBS who have failed to respond to conventional IBS therapy. This cautious approach by the FDA is based on incidents of ischemic colitis that have been identified in patients taking alosetron. The efficacy of alosetron is thought to result from a delay in colonic transit and a decrease in abdominal discomfort during colonic distension. The mechanism(s) underlying the effect of alosteron remains incompletely understood; however, evidence suggests that $5\text{-}HT_3$ receptors are present on afferent nerves. Thus, a reduction in symptoms may occur through a decrease in the activity of central autonomic networks. Another recent therapy designed to treat IBS is tegaserod (Zelnorm), a 5-hydroxytryptamine type 4 ($5\text{-}HT_4$) receptor partial agonist, which possesses promotility effects through the stimulation of intestinal and colonic transit. In preclinical studies, tegaserod reduced afferent firing rates in cats and inhibited visceral sensitivity in rodents. Tegaserod recently received FDA approval for the short-term treatment of women with IBS who have constipation. In clinical trials, tegaserod was more effective than placebo at relieving global IBS symptoms in female patients with constipation. Tegaserod also significantly improved abdominal discomfort, bloating, and constipation. Unlike cisapride, cardiac repolarization is unaffected by tegaserod and thus is not associated with potential life-threatening cardiac arrhythmias.

To improve pharmacological treatment of patients with IBS, a strong scientific rationale exists to examine the effectiveness of other agents targeted toward specific neurotransmitter systems involved in the brain–gut axis. Newer generation anticholinergics that selectively antagonize the muscarinic $M_3$ receptor, as well as selective antagonists of neurokinin receptors ($NK_1$, $NK_2$, and $NK_3$), corticotropin-releasing factor receptor type 1, somatostatin, and cholecystokinin receptor, may reduce the symptoms of IBS. Finally, as knowledge of the role of intestinal microflora grows, future approaches for the treatment of IBS to reduce pain and abdominal bloating may include dietary supplementation with prebiotics or probiotic bacteria to enhance the levels of specific, beneficial intestinal bacteria, such as *Lactobacillus plantarium 299* and *casei GG* or *Bifidobacterium infantis*. However, to date, the evidence in support of probiotic bacteria for the treatment of IBS remains controversial and requires further investigation.

## FINAL COMMENTS

Substantial progress has been made in understanding the effective pharmacological approaches to the treatment of GI disorders. Future research needs to be directed at better defining GI physiology and pathophysiology so that current treatment approaches can be modified and new therapies that possess enhanced efficacy and fewer side effects can be developed.

### Acknowledgment

Thanks are extended to the Presbyterian Health Foundation and the Veterans' Affairs Research Foundation for their continued support.

### See Also the Following Articles

**Antacids • Anti-Diarrheal Drugs • H2-Receptor Antagonists • Laxatives • Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) • Over-the-Counter Drugs • Probiotics • Proton Pump Inhibitors**

### Further Reading

Berman, S. M., Chang, L., Suyenobu, B., Derbyshire, S. W., Stains, J., Fitzgerald, L., Mandelkern, M., Hamm, L., Vogt, B., Naliboff, B. D., and Mayer, E. A. (2002). Condition-specific deactivation of

brain regions by 5-HT3 receptor antagonist Alosteron. *Gastroenterology* 123, 969–977.
Bombardier, C. (2002). An evidence-based evaluation of the gastrointestinal safety of coxibs. *Am. J. Cardiol.* 89, 3D--9D.
Brandt, L. J., Locke, R. G., Olden, K., Quigley, E., Schoenfeld, P., Schuster, M., and Talley, N. (2002). An evidence-based approach to the management of irritable bowel syndrome. *Am. J. Gastroenterol.* 97, S1–S26.
Campieri, M. (2002). New steroids and new salicylates in inflammatory bowel disease: A critical appraisal. *Gut* 50, III43–III6.
De Vos, M. (2002). Standard and innovative therapy of inflammatory bowel diseases. *Clin. Exp. Rheumatol.* 20, S95–S100.
Elson, C. O. (2002). Genes, microbes, and T cells: New therapeutic targets in Crohn's disease. *N. Engl. J. Med.* 346, 614–616.
Floch, M. H., and Narayan, R. (2002). Diet in the irritable bowel syndrome. *J. Clin. Gastroenterol.* 35, S45–S52.
Madden, J. A. J., and Hunter, J. O. (2002). A review of the role of gut microflora in irritable bowel syndrome and the effect of probiotics. *Br. J. Nutr.* 88, S67–S72.
Wingate, D., Phillips, S. F., Lewis, S. J., Malagelada, J. R., Speelman, P., Steffen, R., and Tytgat, G. N. (2001). Guidelines for adults on self-mediation for the treatment of acute diarrhea. *Aliment. Pharmacol. Ther.* 15, 773–782.

# Physiologic Ileus

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**interdigestive state** Physiologic conditions in the digestive tract in the time between completion of digestion and absorption of a meal and the ingestion of the next meal.
**migrating motor complex** A specific pattern of small intestinal motility that begins when digestion of a meal is complete and ends with intake of the next meal. Also called interdigestive motility.
**paralytic ileus/adynamic ileus** A condition in which the prolonged absence of intestinal motility is pathologic.

**Physiologic ileus is the term used to describe the normal absence of motility along a length of intestine. It reflects the operation of one of the neural programs in the spectrum of programs present in the enteric nervous system. Physiologic ileus is a fundamental behavioral state of the intestine in which quiescence of motor function is neurally programmed. For example, in the interdigestive state, the musculature of the small intestine is quiescent except in a limited region where the activity front of the migrating motor complex is present.**

## NEURAL MECHANISM

The state of physiologic ileus disappears following ablation of the enteric nervous system. In situations in which enteric neural functions are blocked by anesthetics or in patients in which pathological factors have destroyed the enteric nervous system, contractile behavior that is disorganized and nonpropulsive occurs continuously.

Physiologic ileus requires the continuous activity of subpopulations of inhibitory motor neurons that are present in the enteric nervous system. Ongoing discharge of impulses by these neurons releases inhibitory neurotransmitters at neuromuscular junctions and this maintains a state of inhibition in the muscles, which are autogenically active in the absence of neural inhibition. In the absence of ongoing neural inhibition, myogenic pacemakers (i.e., electrical slow waves) evoke contractions with each slow cycle and this results in continuous and uncontrolled contractions. Physiologic ileus refers to the normal state of motor quiescence, whereas the terms paralytic ileus and adynamic ileus refer to conditions in which the prolonged absence of intestinal motility is pathological. Pathological ileus is well known as a consequence of manipulation of the bowel and irritation of the peritoneal membranes during abdominal surgery.

### See Also the Following Articles

**Basic Electrical Rhythm • Enteric Nervous System • Migrating Motor Complex • Toxic Megacolon**

## Further Reading

Cullen, J., Caropreso, D., Hemann, L., Hinkhouse, M., Conklin, J., and Ephgrave, K. (1997). Pathophysiology of adynamic ileus. *Digest. Dis. Sci.* 42, 731–737.

Kalff, J., Schraut, W., Simmons, R., and Bauer, A. (1998). Surgical manipulation of the gut elicits an intestinal muscularis inflammatory response resulting in postsurgical ileus. *Ann. Surg.* 228, 652–663.

Wood, J. (1994). Physiology of the enteric nervous system. *In* "Physiology of the Gastrointestinal Tract" (L. Johnson, D. Alpers, J. Christensen, E. Jacobson, and J. Walsh, eds.), 3rd Ed., Vol. 1, pp. 423–482. Raven Press, New York.


# Pica


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**geophagia** Clay eating.

**pagophagia** Ice eating.

**pica** Persistent eating of nonnutritive substances for a period of at least 1 month, without an associated aversion to food.


**Pica, the persistent eating of nonnutritive substances, without an associated food aversion, occurs in people of all ages and both sexes, particularly in young children and pregnant women. The term "pica" comes from the Latin word meaning magpie, presumably named after this bird's peculiar eating behaviors involving an indiscriminate preference for both foods and nonfoods. The causes of pica are uncertain, thus treatment is difficult. Although pica is not always dangerous, the underlying possible etiologies should be assessed.**


## HISTORY

The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) defines pica as the persistent eating of nonnutritive substances for a period of at least 1 month, without an associated aversion to food. The behavior must be developmentally inappropriate and not part of a culturally sanctioned practice, and severe enough to warrant clinical attention. Some clinicians argue that a diagnosis of pica can include the compulsive consumption of certain foods, blurring the distinction between pica and food cravings. Pica is most frequently reported in pregnant women, patients of lower socioeconomic status, and children. It is also found in some cases of iron-deficiency anemia as well as in deficiencies of other nutrients, such as zinc. In some cultures, pica is considered therapeutic and is used in treating maladies such as anemia and anxiety. Interestingly, the range of reported items of consumption has not changed much during the past four centuries. Pica of dirt and clay was known to the Greeks and the Romans and was recorded in a thirteenth century Latin work. Pica was first addressed in a medical book in 1563, in which geophagia was described in pregnant women and in children.

## EVALUATION

The cause of pica behavior has eluded researchers for centuries. Researchers have described several theoretical approaches that attempt to explain the etiology from nutritional, sensory, physiologic, neuropsychiatric, cultural, or psychosocial perspectives. There have been few epidemiologic studies detailing the prevalence of pica. Estimates have varied widely within a particular population, depending on the criteria used. Studies of pregnant, otherwise healthy women have found pica in approximately 8% of respondents. Many of these patients had low serum ferritin levels, suggesting a link between pica and iron deficiency.

In the absence of complications that might signal abnormal eating patterns, diagnosis depends on self-reporting. Patients are likely to underreport pica behavior because of embarrassment or because they are not aware that such behavior might be worth reporting.

Clinical suspicion is therefore required to diagnose pica in the ambulatory setting. Iron or zinc nutrient deficiencies may be suggestive; likewise, lead or mercury poisoning may lead to the diagnosis of pica. Gastrointestinal complications such as bezoars or obstructions may also suggest pica.

## TREATMENT

Given the difficulty inherent in diagnosing pica and the multitude of possible etiologies, treatment is difficult. Many studies have described diminished pica behavior in patients following iron or zinc replacement to treat low iron or zinc levels, although the empiric evidence implicating zinc deficiency in pica is less convincing than is the evidence for iron. In any case, if iron deficiency leads to pica, then pica behavior should cease once iron is replaced. Cessation of pica behavior with iron replacement may not happen, however, suggesting that continued pica behavior may constitute an addiction or a learned pattern of behavior.

Not all forms of pica are dangerous, and some cases might not require intervention. However, physicians must be prepared for cases of pica in their daily practice. Education about nutrition, along with iron therapy or transfusions, might be the first wave of intervention. Psychological counseling or behavior therapy can also be useful adjuncts. Recently, there has been some evidence that pica is a part of the obsessive–compulsive disorder (OCD) spectrum of diseases. In support of this theory, selective serotonin reuptake inhibitors (SSRIs) have shown some promise. Severe or recalcitrant cases could require referral to a mental health specialist.

Review of the literature on pica confirms just how little is known about this common but commonly missed condition. Its cause is related to many factors, and there are questions about whether pica is a cause of or an effect of metabolic or behavioral states. Accurate diagnosis is hindered by the need for self-reporting on the part of the patient and by a low index of suspicion on the part of the clinician. No specific screening tests for pica exist, but an accurate and timely diagnosis can help to avoid some of the many nutritional, gastrointestinal, and psychological complications. Finally, when pica is diagnosed, there are no proven treatments. Although selective serotonin reuptake inhibitors can be helpful in some cases, diagnosis and treatment must be individualized, and the practicing physician will most likely need to rely on help from mental health professionals.

### Acknowledgment

Adapted with permission from the publisher from Rose, E. A., Porcerelli, J., and Neale, A. V. (2000). Pica: Common but commonly missed. *JABFP* 13, 353–358.

### See Also the Following Articles

**Bezoars • Foreign Bodies • Psychosociology of Irritable Bowel Syndrome**

### Further Reading

American Psychiatric Association (1994). "Diagnostic and Statistical Manual of Mental Disorders: DSM-IV." American Psychiatric Press, Washington, D.C.

Parry-Jones, B., and Parry-Jones, W. L. (1992). Pica: Symptom or eating disorder? A historical assessment. *Br. J. Psychiatry* 160, 341–354.

Rose, E. A., Porcerelli, J. H., and Neale, A. V. (2000). Pica: Common but commonly missed. *J. Am. Board Fam. Pract.* 13, 353–358.

# Picture Archiving and Communication Systems (PACS)

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**analog imaging system** Plain radiograph (e.g., chest X ray, mammogram) scan devices; images are not obtained using digital computer technology.

**archive** Storage of data.

**bit** Binary unit; smallest unit of information used by a computer; 8 bits equals 1 byte.

**computed radiography** System using computers to capture and digitize an image rather than print it on film.

**digital display protocol** Preselected method of displaying a patient's new and old radiographic images.

**digital fluoroscopy** Capturing and transmitting fluoroscopy information to a computer rather than intensifying it and using it to expose film.

**digital images** Binary-coded representations that can be interpreted by a computer and displayed on a monitor.

**ergonomics** Design of environment or equipment related to natural body position and physical comfort.

**film digitizer** Machine containing a laser that converts analog information on conventional film into digital data, which can be stored in a computer and displayed on a monitor.

**film file room** Place where X rays are stored.

**film screen** Combination of silver-coated photographic film layers, sensitive to X rays only, enclosed in a light-proof cassette.

**gigabyte** One billion ($1 \times 10^9$) bytes.

**graphical user interface** Setup that allows humans to interface with software, using words, pictures, and computer tools (keyboard and mouse); a workstation monitor, for example, on which two-dimensional and three-dimensional images are manipulated.

**hardware components** Computers, monitors, printers, and any other peripheral computer-connected devices.

**hospital information system** Computerized system containing patient medical and personal identity information.

**imaging device** Machinery that scans and captures body images (as in computer tomography, magnetic resonance imaging, radiography, and fluoroscopy).

**image fusion** Digital overlap of data from different types of images.

**image noise** Information that interferes with interpretation of utilizable data.

**imaging plate** System analogous to silver nitrate film, but using phosphorescent technology to capture images digitally, rather than converting silver to form an image.

**image resolution** Degree to which very small objects located in close proximity can be distinguished in an image.

**lossless compression** Method to compress digital data without losing critical information.

**lossy compression** Method to compress voluminous data with some loss of information.

**network** Interconnected computer systems (for example, in a hospital or community health care system).

**open architecture** Network design that allows interconnected components to communicate using the same standards and language.

**operating system** Programs (software) that determine the functions and abilities of a computer; disk operating system (DOS) (examples include Windows 95 and Apple DOS).

**pixel** Picture element.

**processing speed** Time it takes a computer to accomplish a given task.

**radiology information system** Computerized system used for scheduling and storing pertinent patient data.

**region of interest** Area indicated by a circle or square on a cross-sectional image in which the computer is programmed to display a reading that may indicate a solid or fluid component.

**storage archiving units** Disks that are recorded and read using laser light (examples include read-only memory compact and digital video disks).

**telecommunications** Transmission of sounds, images, and digital data using electrical and computer technology.

**three-dimensional computed tomography angiography** Three-dimensional reconstruction of blood vessels, extracting background data from conventional computed tomography images to allow images to appear as if they were simply an angiogram.

**three-dimensional rendering** Computer reconstruction of two-dimensional data to appear as though three-dimensional.

**virtual colonoscopy** Three-dimensional images of the colon, simulating an endoscopic view, created using information obtained from a computer tomography scan.

**A picture archiving and communication system is a network of computers and imaging devices, databases, storage devices, and display monitors, all of which communicate with one another throughout a hospital, health**

 

network, or community to store, transmit, and display digital images and patient information in a rapid and convenient manner. The system eliminates conventional hardcopy film and replaces the conventional film file room and associated personnel, avoiding the inadvertent duplication and loss of information associated with an analog imaging system. A fully networked hospital-wide system facilitates simultaneous image viewing and consultation of radiographic studies by, for example, a surgeon in the operating room, a radiologist in the reading room, and an oncologist in the clinic. The system incorporates the hospital information system and radiology information system for seamless data transmission, billing, and patient scheduling.

## BRIEF HISTORY

Great technological advances in the past century that set the stage for the creation of picture archiving and communication system (PACS) have included the development of digital fluoroscopy, digital image systems, computed radiography, high-resolution (2048 × 2048 pixels × 12 bits) liquid crystal display flat-screen monitors, personal computers with high-capacity memory, self-contained units using dry film and laser technology, and gigabyte-speed Ethernet wide area networks has enabled systematic linkages of picture archives and communication.

Dr. Paul Capp introduced the concept of digital radiology in the early 1970s. Soon after, the invention of computed tomography (CT) by Godfrey Hounsfield represented a landmark advance in imaging science. CT introduced cross-sectional imaging, but also demonstrated the value of computers in image production. Plain radiography (film screen) and its associated shortcomings, including inability to change the image once the film is exposed, inability to view the film at multiple locations, and inefficiency of manual filing and retrieval of films, are well-known to radiologists. The development of imaging plate (IP) systems (based on photostimulable phosphor technology) in the late 1970s and early 1980s allowed for replacement of film-screen imaging and creation of computed radiography (CR) in 1987. Concurrent with these advances, computer technology evolved rapidly, with increases in processing speed, more powerful operating systems and graphical user interfaces, increased storage capacity, and decreased cost. Finally, the development of the first film digitizer and large-capacity optical storage disk by Kodak further provided essential components for PACS development. Eventually, storage devices, essentially redundant arrays of inexpensive disks (RAIDs, see later), were created.

The first international conference and workshop on PACS for medical applications took place in January 1982, sponsored by the International Society of Optical Engineering (SPIE). At the time, however, much of medical imaging technology had yet to be developed. During the 1980s, Ethernet, a local area network (LAN) communications system via coaxial cable radiofrequencies, became a telecommunications standard, with data transmission rates quickly maturing from 1 megabyte per second to the current 100 megabytes per second (gigabyte Ethernet). Concurrently, data compression was created as an alternative way to speed network delivery. Lossless compression rates of 3 : 1 have evolved toward lossy compression techniques promising rates on the order of 20 : 1 or 30 : 1. The American College of Radiology and National Electrical Manufacturer's Association (ACR-NEMA) group proposed standards for communication of medical images over networks, which became official in 1985. These limited standards were revised in the 1990s into the Digital Imaging and Communications in Medicine (DICOM) standard to embrace traditional computer networks. The saga of PACS development continues as technology improves and various companies have begun to offer fiber-distributed data interfaces (FDDIs), T3 lines (carrying large-bandwidth signals on fiber-optic cable), and asynchronous transfer modes (ATMs), an international standard adopted by the telecommunications industry, promising memory-to-memory transfer rates of 2.4 gigabytes per second.

## GENERAL PRINCIPLES

PACS consists of image acquisition devices [e.g., computed radiography/tomography and magnetic resonance imaging (MRI) scanners], storage archiving units (e.g., RAIDs, optical disks, read-only memory digital video disks), display workstations, computer processors, and databases. A communications network and a database management system integrate these components. The hardware components are integrated by standardized, flexible software systems for communications, error handling, database and storage management, job scheduling, interprocessor communication, and network monitoring (Fig. 1).

PACS must include system standardization, open architecture, connectivity, reliability, and security. System standards might include UNIX and Windows NT operating systems, transmission control protocol/Internet protocol (TCP/IP), DICOM communication protocols, structured query language, ACR-NEMA and DICOM image formats, C and C++ programming languages, X Window user interface, American

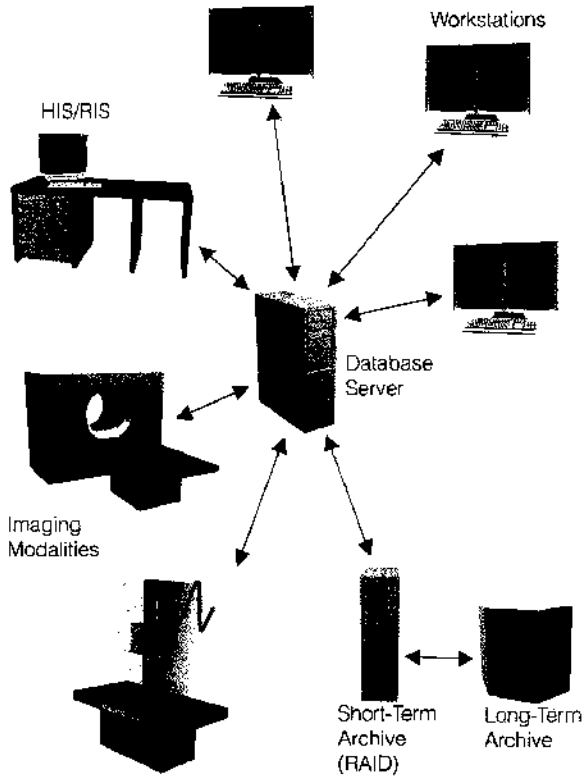


FIGURE 1 An example of a basic PACS configuration. HIS, Hospital information system; RIS, radiology information system; RAID, redundant array of inexpensive disks. © ECRI (2000). Reprinted with permission from *Health Devices* 2000 Nov; 29(11): 387.

Standard Code for Information Interchange (ASCII) text representation for message passing, and health level-7 (HL-7) for health care database information exchange.

Open architecture and connectivity describe a system in which components that are to be connected are able to "speak" to one another in the same "language," so that they are not isolated. They can also be simultaneously upgraded. Reliability (thus high "up time") is critical to patient care. Extended periods of down time cannot be tolerated. Systems must use fault-tolerant measures, including error detection and logging software, external auditing programs, and hardware redundancy. Finally, security is important in the realm of medicolegal and patient confidentiality issues. Violations can include physical intrusion and misuse of privilege.

Image compression is used in PACS to decrease data storage and transfer requirements and to increase data transfer speed. Compression can involve either no loss of information (lossless) or reduction of data with preservation of important information (lossy). Typical acceptable data compression ratios used today are 3 : 1 using the Joint Photographic Experts Group (JPEG) file format, which is DICOM compatible. Wavelet transform can allow higher rates of compression, but is not currently DICOM compatible. Image compression has become a more important issue with the emergence of thinner and more voluminous multislice CT data sets. Megibow *et al.* recently evaluated the ability to diagnose appendicitis, depending on the amount of lossy wavelet compression from 8 : 1 to 24 : 1. Beyond 8 : 1, sensitivity and eventually accuracy (at 24 : 1) decreased, suggesting that finite levels of wavelet transform may be applied to CT images without compromising diagnostic performance.

Using effective networking, many components can be interconnected in PACS. This capability is a key feature of PACS and is facilitated by the DICOM communication standard developed by ACR-NEMA to allow the sharing of information using products from different suppliers. Networks vary according to data transmission methods, architecture of the network hardware, image distribution methods, and image identification and retrieval methods. Typical setups include (1) a regular Ethernet LAN between the image modality device and the image acquisition gateway (low speed; 10 megabits/sec, because the CT scanner is slow to generate images), (2) an Ethernet or FDDI (medium speed; 100 megabits/sec) or ATM (high speed; 155–622 megabits/sec) between the gateway and the PACS controller, and (3) an ATM or FDDI between the PACS controller and the display workstations, because clinicians must access images at a rapid rate.

Network hardware architecture may be centralized (a central location for all images, with direct high-speed links to any workstation at any time), local (tailored to a specific modality, e.g., ultrasound miniPACS), or distributed (in which local modality archives—CT, MRI, and ultrasound (US)—are connected by a high-speed standardized network). Each of these network organizations has advantages and disadvantages regarding cost and demands on the server.

Image distribution methods include on-demand and routed (cached). An on-demand system allows a user to log on and access any image from any workstation (usually in centralized systems). In routed systems, studies are stored locally at a workstation or at specified workstations, but not at all of them. An example of a centralized, on-demand type system (Fig. 2) is the General Electric Pathspeed PACS. Images are sent from an imaging modality to a central database server and then to a central archive (e.g., a RAID) for short-term memory (images are typically copied from the RAID to long-term storage as well). When a user selects a study at a workstation, it is sent from the RAID to the workstation's

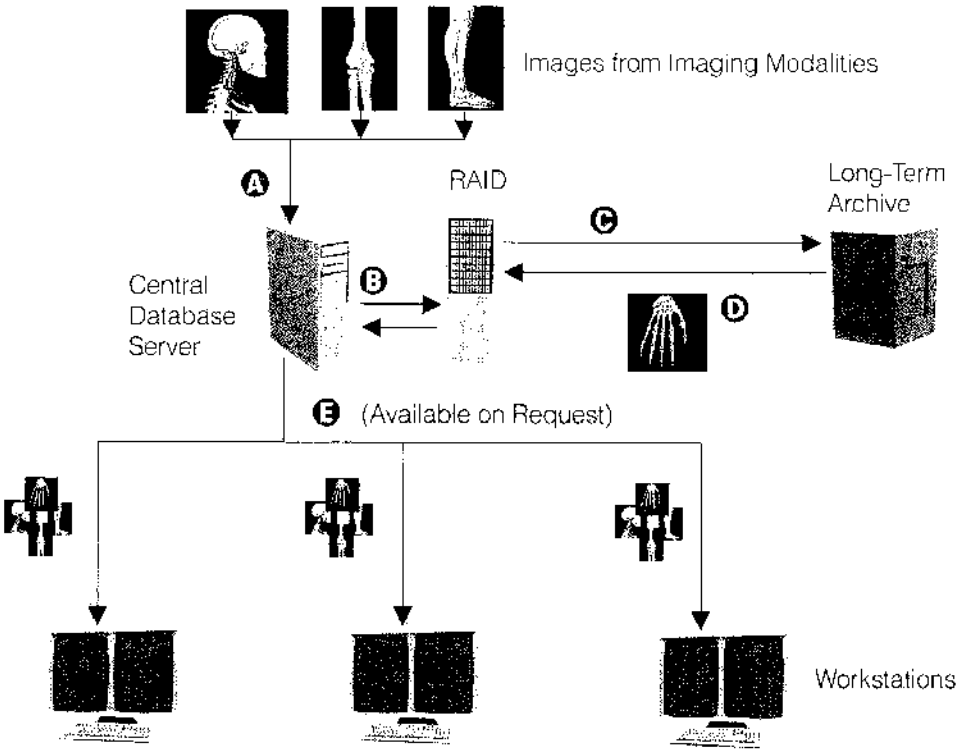


**FIGURE 2** Simplified representation of the workflow in a PACS that uses an on-demand image distribution method with a centralized architecture. (A) Images are sent from an imaging modality to a central database server, which in turn (B) sends the images to a redundant array of inexpensive disks (RAID). (C) At this point, images may also be copied to the long-term archive. (D) Images requested from the long-term archive, either those retrieved before the procedure or those requested by the user at the workstation, are also moved to the RAID. (E) Users at any workstation can query the database server to receive any image in the system. © ECRI (2000). Reprinted with permission from *Health Devices* 2000 Nov; 29(11), 395.

memory. When a user updates a study, the updates are sent back to the RAID (and also copied to long-term storage). Similarly, when a user requests a study from the long-term archive, it is sent from there directly to the RAID and then routed to the user's workstation. This same process occurs in "prefetching," whereby PACS automatically retrieves relevant studies from the long-term archive when a patient is admitted or scheduled at the radiology information system (see later). One drawback of centralized versus distributed systems is that a system failure of the central database disables the whole PACS. However, PACS today have significant built-in redundancy to prevent such system-wide failures.

## ANATOMY OF PACS

### Input

The database server and archive system together comprise the PACS controller. The controller organizes data from multiple sources into a coherent package. It acquires images, archives them, and distributes them to display workstations and processes image retrieval requests. PACS can also be interrogated in order to retrieve images, review patient and study information, study practice statistics, and perform outcomes analysis.

Images from the acquisition devices (e.g., CT, MRI, and CR scanners) and from devices that convert analog images to digital images (digitizers), as well as pertinent patient information, arrive at the acquisition gateway computer (AGC). The job of the AGC is to receive images from the respective modality components, extract text information describing the received study, update the database management system, determine the destination workstation, automatically retrieve necessary comparison images, determine optimal contrast and brightness parameters for display from lookup tables for cross-sectional modalities (e.g., window and level), perform image data compression, archive new studies onto the optical disk library, and service archive retrieval requests from workstations and other PACS

controllers. The AGC ensures the integrity of image data at various points along the path. At the imaging device, an image will not be deleted from the local storage device until verified by a technologist that it has been archived via the PACS connections. At the AGC, images remain on the local magnetic disk until the archive subsystem acknowledges that a successful archive has occurred, at which time space is made on the disk and these are cleared. At the PACS central node, images arriving in the archive server from various nodes are not deleted until permanently archived.

Other sources of information arriving at the database server of the PACS controller are the hospital information system (HIS) and radiology information system (RIS). The HIS serves three functions: (1) it supports clinical and medical patient care activities in the hospital, (2) it facilitates administration of the hospital's daily business transactions, including financial, personal, payroll, and bed census, and (3) it assists the evaluation of hospital performance, costs, and long-term forecast projections. RIS manages patient demographics, billing, procedure descriptions, scheduling, diagnostic reports, patient arrival scheduling, film location, film movement, and exam room scheduling. It consists of a computer system with peripheral devices such as alphanumeric terminals, printers, and bar code readers. Using the HL-7 standard, scanning a simple bar-code entry can download the relevant data from the RIS to the acquisition unit, which would then incorporate the data into the DICOM packet with the image.

RIS/HIS interfacing occurs using a standard Ethernet. Information and messages concerning patient admission, discharge, and transfer are sent to PACS only when a patient is scheduled for an examination in radiology. An HL-7 standard data format is used running on TCP/IP communication protocols. Prefetching is also initiated as soon as HIS/RIS gets an admission, discharge, or transfer message. Prefetched data are sent to display workstations prior to current exam completion. The prefetched algorithm is based on predefined parameters such as examination type, disease category, radiologist, referring physician, and location of display workstation. Integration of these systems into PACS reduces redundant data entry and storage and avoids the expense and clutter of separate office computers, terminals, and workstations.

## Archive

An important advantage of PACS has been the elimination of film. Nonetheless, a busy department can generate many gigabytes ($10^9$) of data per day and several terabytes ($10^{12}$) per year. This presents a technological and economic challenge. Digitized images created over several years can be accessed on a variety of storage media, including magnetic and optical disks and tapes, on "jukebox" systems for storage of multiple disks and tapes.

A tiered approach between short- and long-term methods offers two advantages—cost control and maintaining useful retrieval times based on likelihood and immediacy of need; less expensive storage media can be used for long-term storage because the level of functionality required is less than that needed for short-term storage. Short-term storage, usually accomplished using RAIDs, can involve storing studies for only a few weeks; users can specify any length of time. The demand for rapid display of images at the display workstation is well served by RAIDs, whereby multiple disks are accessed to aggregate data fragments. As the cost of RAIDs decreases there is a greater tendency to use this method for intermediate and even long-term storage, allowing images to be retrieved quickly regardless of when they were archived.

To provide both temporary and permanent storage, long-term archive employs a variety of media, including magneto-optical disks and read-only memory compact and digital videodisks. Typically, PACS copies images to both short-term and long-term storage immediately to protect from loss of short-term memory in a system failure. Images in short-term storage are removed once they have been read.

## Output

With PACS, film is no longer the medium of the radiologist. The image output is to a display workstation or to an inexpensive paper printer. This reduces costs associated with film, chemicals, film storage, and film management. Different display workstations offer various levels of functionality, resolution, and other display characteristics and can meet the needs of different users. From prior surveys, radiologists have deemed most important the ability to compare new with old studies, and rapid access to images. Certain workstation display features are considered standard, such as zooming, changing window and level, rotating an image, and obtaining density measurements. Each display workstation consists of a host computer and an image display board, a display video monitor, and a local storage device.

Workstations will differ in their physical (spatial resolution, focus, luminance, computation speed, local storage space, bus speed, and network access speed) and functional (software capabilities and human–computer interface) requirements. Important features include ergonomics, lighting conditions,

glare, and acoustic noise from hardware. A key issue determining workstation quality is image resolution. Resolution increases with an increased number of pixels. Bit depth (number of bits/pixel) is another important feature in grayscale depiction. Although 12 bits/pixel is standard for CT/MR and CR for all tissues, US requires only 8 bits/pixel. The development of monitor technology to overcome limitations and inadequacies for the accurate display of mammograms and skeletal radiographs has been a challenge.

Six types of workstations can be described: diagnostic, review, analysis, digitizing and printing, interactive teaching, and desktop. At a diagnostic workstation, radiologists make primary diagnoses using the best resolution possible. This includes 2K (K = 1024 linear pixels; 2048 × 2048 pixel imaging array) monitors for plain radiography (necessary for analysis of fine detail) and 1K (1024 × 1024 pixels) monitors for CT and MR. At the diagnostic monitors, a digital Dictaphone may be available. A worklist may also be available to include all studies that meet the user's selection criteria, e.g., body-MR cases. The user also can choose how to arrange the images on the monitor, including positioning of old studies, using various digital display protocols (DDPs). The resolution of review workstations in clinics and hospital wards need not be as high, because cases are primarily being reviewed after they have been interpreted, and not every minute detail need be observed.

Analysis workstations are packaged with specialized image analysis software; they can perform, for example, three-dimensional rendering, image fusion, and color enhancement. Models include the GE Navigator software for virtual colonoscopy and Vital Images Vitrea software for three-dimensional CT angiography. A digitizing and printing workstation is used by the film file room personnel to digitize historical films or films acquired outside the hospital. Elimination of film is the ideal objective of PACS, but sometimes hardcopy images will be necessary. This is accomplished with a multiformat camera and laser film, a laser scanner, and a laser or paper printer. Interactive teaching workstations emulate the role of teaching files in the film library, but with more interactive features. Finally, a desktop workstation is used to generate lecture slides and teaching and research material from images on PACS. This is done at a personal computer and requires only a 512 × 512-pixel monitor.

## WORKFLOW SCHEMA

In a film-based department: a procedure is scheduled and patient data are entered in the RIS. Before the patient arrives, the film file room personnel retrieves prior studies for that patient and sends them to the radiologist's reading room. When the patient arrives for the study, the identifying data are reentered into the imaging modality. The patient is scanned and films are exposed at the modality. These are developed and brought to the reading room for posting on a film alternator. These are read while also reviewing prior images. If additional prior imaging studies are needed, the radiologist requests these from the file room. Once they arrive, the radiologist finishes the case and dictates a report. A transcriptionist types the dictated report and sends a printed report to the radiologist, who edits it as necessary. Once revised by the transcriptionist, the report is sent to the referring physician. This whole process may take 3–4 days.

After full PACS implementation, the workflow would proceed as follows: scheduling information and patient data are entered in the RIS and sent to the relevant imaging modality automatically. Before the patient arrives, PACS automatically retrieves prior studies from its long-term archive based on the information in the RIS and the rules established. The images are made available in local storage for ready access. At the scheduled time, the patient is imaged and digital images are transmitted immediately to PACS. These are read along with relevant prior images at a PACS workstation. Images can be easily adjusted for improved viewing or analysis. Radiologists at other locations can be consulted on the same study if necessary. If older studies are needed, they can be accessed from long-term storage within a few minutes. When review is complete, a report is dictated using speech-recognition tools. The radiologist edits the electronic report directly and sends it to the referring physician immediately through RIS or e-mail. This can take several hours or less from start to finish.

## ADVANTAGES

### General

As a new and evolving costly technology, PACS will need to undergo formal critical evaluation by physicians, the health care system, and society. The methodology for doing this has been set forth by Fryback and Thornbury. Categories of evaluation include safety, technical efficacy, diagnostic accuracy efficacy, diagnostic thinking, therapeutic efficacy, patient outcome efficacy, and societal efficacy.

Widely publicized studies from the hospital of the University of Pennsylvania in the early 1990s demonstrated a statistically significant reduction in time spent

TABLE I Summary of Benefits of the Picture Archiving and Communications Systems[a]

| Category | Benefit |
|---|---|
| 1 | **Benefits to the diagnostician** |
| | Improved access to current patient records |
| | Improved access to patient history records |
| | File integrity and speed of retrieval |
| | Better diagnosis |
| | Quicker diagnosis/improved productivity |
| 2 | **Benefits to the referring physician** |
| | Better patient management/earlier intervention |
| | Better patient outcome |
| | Reduced length of stay |
| | Reduced legal costs arising from maladministration claims, based on loss of films, lack of patient history, etc. |
| 3 | **Benefits to the patient** |
| | Reduced radiation exposure from X-ray equipment |
| | Shorter examination times |
| | Reduced radiation exposure as a result of less need for retakes of images |
| | Reduced patient inconvenience in attending hospitals for examination and reexaminations |
| | Reduced chance of adverse reaction to contrast agents |
| 4 | **Benefits to the hospital** |
| | Better communication with physicians |
| | Better hospital administration |
| | Better training of radiology and other students through access to on-line image files and to digital teaching files |
| | Greater staff retention due to improved morale |

[a] Data reprinted with permission from Crowe (1992).

by clinicians performing clinical activities when images were available on digital display, compared with traditional film retrieval protocols. Imagine the advantages in gastrointestinal radiology if more immediate clinical action could be taken in cases of bowel obstruction, perforation, gastrointestinal bleeding, ischemia, postoperative leaks, and the like. Other studies looking at time savings have shown that nonphysician employee staff can be reduced 26% and that significantly increased time is available to technologists when film handling is eliminated. The overall benefits to the diagnostician, referring physician, patient, and hospital are summarized in Table I. In a practice of gastrointestinal radiology, PACS can facilitate daily practice in both fluoroscopy and cross-sectional modalities.

## Gastrointestinal Fluoroscopy

Fluoroscopy is a unique modality that involves the hands-on, potentially time-intensive radiological examination of a patient with repeated and continuous radiation exposure (at the radiologist's discretion). A constantly moving tube (because of peristalsis) is being examined within the patient. Characterization of this is useful in addition to information gained from static images. Intermittent distension and collapse of the bowel and variable progression of administered contrast through the gastrointestinal tract limit the examiner. The window of opportunity to capture time-dependent changes can be missed or capitalized on in a manner quite unlike the radiological examination of any other organ system.

Examining the patient using digital technology and PACS, compared to film, allows more rapid and well-timed exposure and capture of pertinent information because a cassette is not mechanically moving into place. Acquisition of rapid-sequence digital exposures (8/sec) also becomes possible (versus mechanically derived exposures of 100-mm film, limited to 3/sec). Digital exposures can be immediately reviewed on the monitor before fluoroscopy resumes. The adequacy of each film can be immediately assessed, and assessed sooner en masse, compared to cassette film. Immediate supervision of residents can be done for quality control and can minimize the number of errors caused by technically suboptimal exams. The immediate or rapid availability of old studies and correlative modalities enables very quick answers to any queries and allows reexamination while the patient is still in the department; this is a very problem-oriented and tailored approach. Waiting for development of spot radiographs is avoided, eliminating the long delays that may prevent reexamining a patient, only to find suboptimal coating and distension. Finally, compared to conventional fluoroscopic equipment, digital technology allows lower radiation exposure, depending on the number of exposures, the use of pulsed fluoroscopy, and screen capture.

Immediate image review has practical benefits. In cases in which overheads are not required, patients need no longer wait in the department while a series of cassettes is developed in a film processor. They can leave immediately after review of spot films on the workstation. This also frees up the room and the technologist more quickly, further expediting overall throughput. Significant advantages are also available during final film readout sessions at the PACS monitor. Old studies are readily available for comparison. Even old studies, performed at an outside hospital but pertinent to the current fluoroscopic studies, can be digitized in advance for later review. In addition, immediate side-by-side correlative modality comparison (to CT, MRI, PET, etc.) is a useful educational tool in gastroenterology, because the study is often being performed as followup to questionable findings on cross-sectional studies.

This process may also allow demonstration of findings more rapidly.

The software tools available at the workstation monitor allow control of brightness, contrast, magnification, and edge enhancement so that a granular or reticular mucosal pattern or small polyps or ulcers may be more easily seen. Small postoperative leaks and extraluminal gas collections may be made more apparent with these adjustments as well. The scrolling function allows scrolling through captured rapid-sequence studies for a dynamic effect and avoids obtaining more films.

PACS has improved the efficiency of communication and reporting of results to referring clinicians. Placing arrows and annotations to mark significant images allows a quick review of the pertinent findings by clinicians at remote display monitors. PACS makes a positive contribution to teaching and learning. More images can be displayed more quickly without the burden of handling many films. Residents and fellows can scroll through these images to arrive at a better gestalt for the abnormality. Instead of displaying suboptimal copy films on a light box, digital images (which can be manipulated) are automatically accessible and can be viewed and demonstrated in a conference room from a PACS monitor connected to audiovisual equipment. This facilitates better visualization for all residents/fellows in the conference room, rather than the few sitting up front or actually "taking the case."

PACS can also assist in research and publication efforts. It allows more efficient collection of similar cases, by saving them in a teaching folder in the PACS module/worklist. In the academic setting, using a personal computer web browser or workstation, production of slides quickly and without loss of image quality is an added benefit for both teaching files and publication uses. Finally, teleradiology has great potential for aiding consultations and extending expertise around the world.

## Cross-Sectional

The contribution of PACS to the capture, transmission, and display of images from cross-sectional modalities has been nothing short of revolutionary. If "a picture is worth a thousand words," then one can barely do justice trying to express in any amount of words the incremental advantages of displaying a 500-"picture" MRI study on soft copy, versus on innumerable pages of laser-printed film. For example, viewing images in a rapid sequential manner on PACS offers a teleological three-dimensional gestalt that cannot be achieved with film reading. In PACS, the imaging specialist has the ability to scroll or cineloop through images and mentally reconstruct anatomy and pathology, based on training and experience. Stated in another way, many structures are anatomically aligned more longitudinally in the body, such that interpretation of axial images gives an incomplete picture of the overall organ or process. Radiologists have all had the experience of deciding if a dot is a lung nodule or lymph node based on whether it is visible on several slices above and below (is longitudinally continuous and therefore a vessel or other tubular structure), or is isolated to that slice (real pathology). Scrolling allows more rapid assessment of longitudinality. When dealing with the alimentary tract, not only is tracing the course of the colon facilitated, but an orderly tracing of the entire small bowel can be nearly achieved. Localizing obstructions and masses, intussusceptions and even accurately identifying the course of bowel and its relationship to adjacent structures become more reliable. The teleologically gifted can often draw a coronal "road map" for the surgeon after viewing the intestines in this manner. The use of specialized display workstations (e.g., GE Advantage Windows 3.1) to reformat images into coronal or sagittal views or create angled multiplanar reconstructions may assist with these tasks as well.

In the solid gastrointestinal tract (liver, gallbladder, pancreas, and intestinal mesentery), PACS offers advantages in image manipulation, archive, volume handling, and image viewing. Manipulation of images may include distance measurements, volumes (tumor burden changes with treatment, liver transplant volume estimation, lung reduction surgery evaluation, etc.), region of interest density measurements, and magnification/minification. In addition, the window and level can be easily adjusted to the observer's liking. Annotations using arrows and text can be added, and significant images can be marked for later reference or remote conferencing with other interested clinicians.

Image archive is now digital. It is not necessary to look through an entire film folder for old/misplaced/jumbled CT examinations. All prior studies are available either in short-term (prefetched) or long-term archive, which may take 1–2 minutes to retrieve, saving time and manual labor. Comparison with other types of studies is also facilitated. This efficient, invaluable process has the potential to help us learn how to better interpret various studies—in a sense, providing personal quality control.

The volume of images in a PACS folder may challenge memory capacity, depending on image compression types and ratios, but still represents a major advantage over film. Filming extra sequences (delayed images, thinner slice reconstructions, coronal or other reformats, etc.) no longer requires using more

film and personnel time, both valuable and expensive resources, but rather merely requires sending the images to PACS.

Viewing images is facilitated with PACS. Any two images from any study and any date can be placed directly next to one another. This can be accomplished with preset digital display protocols. These DDPs can be personalized and saved and shared among different users. The scrolling function, in addition to being useful in distinguishing longitudinally oriented structures from lymph nodes or lung nodules, can also be used to simulate motion in vascular perfusion studies. Finally, the timely arrival of PACS has facilitated the viewing of large data sets associated with virtual colonoscopy.

Some difficulties, disadvantages, and pitfalls have been found with PACS. Several institutions have initially found that cost savings for film attributable to PACS can be largely offset by PACS equipment maintenance costs. On the other hand, cost effectiveness also varies with intangible benefits, such as referring physicians' and support staff productivity gains. Pitfalls in PACS are usually a result of human error, whereas bottlenecks are due to imperfect design. Three errors involving the acquisition device are entering the wrong input parameters, stopping an image transmission process improperly, and incorrect patient positioning (in CR, the most common error occurs when the technologist places the imaging plate under the patient in the wrong direction).

A recent United States Department of Defense survey of PACS deficiencies at 14 sites found that the components most commonly cited for deficiencies were the radiologist's workstation (25%), the HIS/RIS/PACS broker interface (16%), the RIS (14%), monitor displays (10%), and the web-based image distribution systems (6%). Larger systems had more failures than smaller ones.

## FUTURE DEVELOPMENTS/SUMMARY

PACS originated as an image management system for improving the efficiency of radiology practice. It has evolved into a hospital-integrated system dealing with information media in many forms, including voice, text, medical records, images, and video recordings. To integrate these various types of information requires the technology of multimedia: hardware platforms, information systems and databases, communication protocols, display technology and system interfacing and integration.

Future developments may include enterprise- and community-wide image distribution systems to balance workload and maximize scarce professional resources, improvements in the quality of service to referring physicians with web-based information distribution systems, wavelet compression techniques, flat-panel monitors, reduced cost of RAIDs, analysis workstations on every monitor, seamless incorporation of HIS/RIS, voice-recognition and computer-automated detection software, and temporal image database management systems to perform outcomes analysis (for example, in lung cancer screening studies by extracting volumes of lung nodules in longitudinal scans).

### See Also the Following Articles

**Computed Tomography (CT) • Magnetic Resonance Imaging (MRI) • Ultrasonography**

### Further Reading


Arenson, R. L., Sehadri, S. B., Kundel, H. L., *et al.* (1988). Clinical evaluation of a medical image management system for chest images. *Am. J. Roentgenol.* **150**, 55–59.

Beall, D. P., Horton, M. C., Lewis, T. E., Monroe, B. S., Baker, M. S., Sweet, C. F., *et al.* (2001). Department of Defense picture archiving and communication system acceptance testing: Review of results and identification of problem components. *Radiology* (Suppl.) **221**, 275.

Becker, S. H., and Arenson, R. L. (1994). Costs and benefits of picture archiving and communication systems. *J. Am. Med. Informatics Assoc.* **1**, 361–371.

Blaine, G. J., Cox, J. R., and Jost, R. G. (1996). Networks for electronic radiology. *Radiol. Clin. North Am.* **34**(3), 505–523.

Crowe, B. L. (1992). Overview of some methodological problems in assessment of PACS. *J. Biomed. Comput.* **30**, 181–186.

Dwyer, S. J. III. (1996). Imaging system architectures for picture archiving and communications systems. *Radiol. Clin. North Am.* **34**(3), 495–505.

ECRI. Emergency Care Research Institute. (2000). Picture archiving and communications systems. *Health Devices* **29**(11), 385–427.

Fryback, D. G., and Thornbury, J. R. (1991). The efficacy of diagnostic imaging. *Med. Decis. Making* **11**, 88–94.

Honeyman, J. C., Frost, M. M., Huda, W., Loeffler, W., Ott, M., and Staab, E. V. (1994). Picture archiving and communicatons systems (PACS). *Curr. Prob. Diagnost. Radiol.* **23**, 102–158

Huang, H. K. (1999). "PACS. Basic Principles and Applicatens." Wiley-Liss, New York.

Krohmer, J. S. (1989). Radiography and fluoroscopy 1920 to the present. *Radiographics* **9**, 1129–1153.

Levine, M. S., and Laufer, I. (1998). The gastrointestinal tract: Dos and don'ts of digital imaging. *Radiology* **207**, 311–316.

Lou, S. L., Huang, H. K., and Arenson, R. L. (1996). Workstation design: Image manipulation, image set handling, and display issues. *Radiol. Clin. North Am.* **34**(3), 525–545.

Megibow, A. J., Rusinek, H., Macari, M. J., Bennett, G. L., and Israel, G. M. (2001). CT interpretation utilizing compressed image data: Acute appendicitis as a model for assessing diagnostic quality. *Radiology* (Suppl.) **221**, 377.

Saarinen, A. O., Wilson, M. C., Iverson, S. C., and Loop, J. W. (1990). Potential time savings to radiology department personnel in a PACS-based environment. Proceedings of SPIE Medical Imaging IV: PACS System Design and Evaluation, Vol. 1234, pp. 823–831.

# Pituitary Adenylate Cyclase-Activating Polypeptide (PACAP)

JOSEPH R. PISEGNA

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hip (SV1) Incorporates a 20-amino-acid insertion in the third intracellular loop of PAC1.

hip-hop (SV3) Incorporates a 40-amino-acid insertion composed of both the hip and hop cassettes.

hop (SV2) Incorporates a 20-amino-acid insertion in the third intracellular loop of PAC1.

PAC1 Pituitary adenylate cyclase-activating polypeptide type 1 receptor.

**Pituitary adenylate cyclase-activating peptide (PACAP) is the most recently discovered neuropeptide in the vasoactive intestinal polypeptide, secretin, glucagon, and related family of peptide hormones. It is so named because, following its discovery in the rat anterior pituitary, this 38-amino-acid peptide hormone was shown to be a potent stimulator of adenylyl cyclase. This hormone was discovered in 1993 and all of its physiological functions are still not completely understood. Given the distribution of this hormone in the peripheral systems, including the gastrointestinal tract, it would be expected to have a major role in physiological regulation.**

## PACAP HORMONE

### Discovery and Gene Structure

Pituitary adenylate cyclase-activating peptide (PACAP) was discovered by Arimura and co-workers using isolated fractions of ovine hypothalamic extracts that stimulated adenylyl cyclase activity in anterior pituitary cells. PACAP circulates as two biologically active forms, one containing 38 amino acids (PACAP-38) and the other containing 27 amino acids (PACAP-27). There is significant interspecies conservation of the amino acid structure of the PACAP hormone.

The primary sequence of the PACAP hormone has a 68% homology with vasoactive intestinal polypeptide (VIP), therefore PACAP is a member of a broader category of hormones that includes VIP, secretin, glucagon, and growth hormone-releasing factor (GRF). As demonstrated in Table I, there is significant homology amongst these peptides. The three-dimensional structure for hormones in this family also demonstrates similarities. The primary amino acid sequence similarity reflects the close similarity in gene structure among the relatives of PACAP, suggesting a similar ancestral gene and perhaps also gene duplication. The PACAP hormone gene has been cloned in several species, including mice and humans. The human gene is composed of five exons and has a structure that is similar to that of other members of this family of peptides. This close similarity suggests that all of the members of this family of peptides may have originated from a similar ancestral gene through duplication.

TABLE I Alignment of Amino Acid Sequences for PACAP and Related Hormones

| Hormone[a] | Sequence[b] |
|---|---|
| PACAP-38 | **HSDGIFTDSYSRYRKQMAVKKLAAVLGKRYKQRVKNK-NH2** |
| PACAP-27 | **HSDGIFTDSYSRYRKQMAVKKLAAVLG-NH2** |
| VIP | **HSDAVFTDNYTRLRKQMAVKKLNSILNK-NH2** |
| Secretin | **HSDGTFTSELSRLREGARLQRLLQGLVG-NH2** |
| Helodermin | **HSDAIFTYSKLLARLALQKYLASILGSRTSPPP-NH2** |
| Glucagon | **HSQGTFTSDYSKYLDSRRAQDFVQWLMNT-NH2** |
| GRF | **YADAIFTNSYSKVLGQLSARKLLQDIMSRQQGESNQERGARARL-NH2** |

[a]Abbreviations: PACAP, pituitary adenylate cyclase-activating peptide; VIP, vasoactive intestinal peptide; GRF, growth hormone-releasing factor.
[b]Boldface type designates amino acids with complete identity at those positions of the PACAP-38 hormone.

 

### PACAP Hormone Distribution

In mammals, the highest concentration of PACAP is in the central nervous system (CNS). The regions of the brain that appear to have the highest concentration (in the rat) are the paraventricular and supraoptic nuclei within the hypothalamus. It is presumed that PACAP is transported from the hypothalamus to the anterior pituitary, where it can exert its effects on the endocrine system. PACAP-38 immunoreactivity has also been shown to be present in extrahypothalamic sites, such as the substantia nigra, cerebellum, pons, and the paraventricular nuclei of the thalamus. In addition, the spinal cord also contains PACAP that is mainly localized in the dorsal root ganglia and dorsal horn. Outside of the CNS, PACAP is present in the adrenal medulla, where it appears to be a potent stimulator of catecholamine release. PACAP is also present in the enteric neural plexus, where it is an important mediator of gastric acid secretion and intestinal motility.

## THE PACAP TYPE I RECEPTOR (PAC1)

### Cloning, Pharmacology, and Signaling

Through cloning studies, PACAP has been determined to have high affinity for three receptors. The first of these receptors to be cloned was the classical VIP receptor (VPAC1); subsequently cloned were the type I PACAP receptor (PAC1) and the VIP2 receptor (VPAC2). Although PACAP has high affinity for all three receptors, each can be distinguished by their affinities for the ligands VIP, PACAP, and helodermin, as shown in Table II (see also Table III for nomenclature of PACAP and receptors). Interestingly, PAC1 has affinity for only PACAP-38 and PACAP-27.

TABLE II Classification of Receptors in the PACAP Superfamily Based on Relative Affinities to Related Peptides[a]

| IUP[b] nomenclature | Relative affinities |
|---|---|
| $PAC_1$ | PACAP-27 = PACAP-38 ≫ VIP > Helodermin |
| $VPAC_1$ | PACAP-27 = PACAP-38 = VIP ≫ Helodermin |
| $VPAC_2$ | Helodermin > PACAP-27 = PACAP-38 = VIP |

[a] Adapted from Harmer *et al.* (1998).
[b] IUP, International Union of Pharmacology.

Cloning of rat PAC1 cDNA shows that it is homologous to the VIP and secretin receptors. The PAC1 cDNA encodes a 495-amino-acid protein with a molecular mass of approximately 50 kDa. Cloning of the rat PAC1 gene shows that the receptor can exist as one of four major splice variants (Fig. 1). The major difference between these four potential splice variants is the structure of the third intracellular domain. There is a "hip" splice variant (SV1) and a "hop" splice variant (SV2), each with a 20-amino-acid third-loop insertion; a "hip-hop" splice variant (SV3) incorporates a combined

TABLE III Nomenclature for the PACAP-Related Receptor Superfamily in Comparison to Previous Nomenclature and Hormone Affinity[a]

| Receptor type | | | | | |
|---|---|---|---|---|---|
| IUP[b] nomenclature | Previous nomenclature | Selective agonists | Selective antagonists | Fluorescent agonists | Selective antagonists |
| $PAC_1$ | PACAP type I<br>PVR1 | PACAP-38<br>PACAP-27<br>Maxadilan? | PACAP 6–38<br>PACAP 6–27 | Fluor-PACAP | PACAP(6–38) |
| $VPAC_1$ | VIP | [$Arg^{16}$]chicken secretin | | Fluo-VIP | [Ac-$His^1$, D-$Phe^2$, $Lys^{15}$, $Arg^{16}$] |
| | $VIP_1$ | [$K^{15}R^{16}L^{27}$]VIP (1–7) GRF(8–27)-$NH_2$ | | | VIP(3–7) GRF(8–27)-$NH_2$ |
| | PACAP type 2<br>PVR2<br>$VIP/PACAP_1$ | | | | |
| $VPAC_2$ | $VIP_2$<br>PACAP-3<br>PVR3<br>$VIP/PACAP_2$ | Helodermin<br>Ro 25-1553<br>Ro 25-1392 | | | |

[a] Adapted from Harmar *et al.* (1998).
[b] IUP, International Union of Pharmacology.

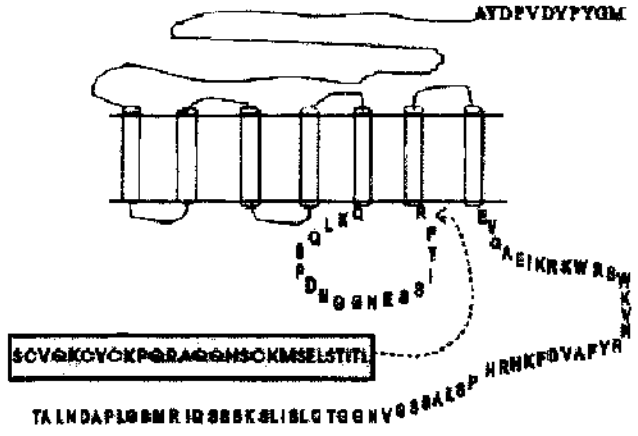

FIGURE 1 Structure of the heptahelical receptor for PACAP, PAC1. The receptor has seven transmembrane domains indicated by the cylinders and a long third intracellular loop. Splice variants are indicated in the shaded rectangle.

40-amino-acid third-loop insertion. These differences in the structure of the third intracellular loop may account for variations in signal transduction coupling to phospholipase C and differences in the tissue distribution of the splice variant. Additional splice variants, affecting either the N-terminus or the second and fourth exons, have also been identified and all of the human PAC1 receptor cDNA splice variants have been cloned. However, unlike the rat splice variants, differences in signal transduction coupling are not observed and the human gene is localized to chromosome 7, whereas in the rat it is localized to chromosome 4. What was observed was a higher efficacy for the hop variant, an intermediate coupling for the hip-hop splice variant, and a lower efficacy of the hip splice variant for coupling to phospholipase C.

The PAC1 receptor, unlike the VPAC1 and VPAC2 receptors, is coupled to a dual signal transduction pathway. A fourth transmembrane splice variant is not coupled to either adenylyl cyclase or phospholipase C yet couples to an L-type $Ca^{2+}$ channel. The region of the native PAC1 shown to be responsible for signal transduction coupling is the COOH terminus, and two amino acids, Ser and Arg, appear to be coupled to signaling.

### Localization of PAC1 Receptors

The PAC1 receptor appears to be expressed in both the CNS and peripheral tissues. In the CNS, the greatest density of receptors occurs in the hypothalamus (i.e., the supraoptic nucleus, periventricular nucleus, and lateral hypothalamus), with the predominant splice variant being the null variant without a splice variant cassette. In the retina, PAC1 has been detected and distributed in the inner plexiform layer. In peripheral tissues, the greatest density of PAC1 is in the adrenal medulla, where the predominant splice variant is the hop type; a similar predominance is found in the anterior pituitary. The human prostate gland contains PAC1 receptors that appear to be up-regulated in conditions such as benign hyperplastic prostate. PAC1 receptors are also present on germ cells of the testis as well as on spermatogonia and Sertoli and Leydig cells. PAC1 and VPAC1 receptors are expressed within the gastrointestinal (GI) tract; the PAC1 receptor is expressed on the gastric enterochromaffin like (ECL) cells and the VPAC1 receptor is expressed on the somatostatin-containing D cells and chief cells of the stomach. The liver appears to contain predominantly VPAC1 receptors. The smooth muscles of the GI tract contain VPAC1 and PAC1 receptors, and the PAC1 receptor has been described in the rat tanei coli. The PAC1 receptor has also been found in macrophages, and other PACAP receptor types have been described in a number of tumor cell lines. PAC1 receptor expression has been reported in human lung and breast cancer cell lines. Differences in splice variant expression of PAC1 receptors in pituitary tumors have also been demonstrated.

## PHYSIOLOGY OF PACAP

### Central Nervous System

Based on the high concentration of PACAP and its receptor, it would be expected that PACAP exerts significant neurophysiological effects. PACAP increases the activity level as well as amount of vasopressin release, and intracisternal administration of PACAP results in the release of gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), prolactin, somatostatin, and the dopamine analogue 3,4-dihydroxyphenylacetic acid (DOPAC). In the pineal gland, there is a high concentration of PAC1, and PACAP can stimulate melatonin secretion. Given its expression in the hypothalamus, another potential action of PACAP is in the control of appetite. In cultured cell systems, PACAP has been shown to activate the c-fos, c-Jun, and mitogen-activated protein (MAP) kinase signaling system, indicating its role in regulating proliferation of cells. In cerebellar granule cells, PACAP appears to reduce apoptosis and have a protective effect against gp120 cultured neuroblasts, again supporting a role for this hormone as a neuroprotective factor.

### Endocrine Organs

PACAP regulates the anterior pituitary to release growth hormone (GH), LH, follicle-stimulating hormone (FSH), prolactin, and adrenocorticotropic

hormone (ACTH). PACAP has been shown to stimulate somatotropic cells that release growth hormone in a way that is additive to the effects of growth hormone-releasing factor (GRF). PACAP acts synergistically with GnRH to stimulate the release of LH and FSH. No direct effect of PACAP has been shown on thyrotropic cells of the pituitary. The second major endocrine site of physiological activity is in the male and female reproductive tracts. PACAP has been localized to the smooth muscles of the female reproductive tract, where it plays a role in muscle relaxation. VPAC2 receptors have been identified in placental tissue, which was the site of initial cloning of the VPAC2 receptor. The ovary contains PACAP in the granulosa zone, where PACAP stimulates progesterone production in the preovulatory phase. PACAP and PAC1 receptors are expressed in large numbers in the male gonadal germ cells, and PACAP stimulates testosterone release in the epididymis and is involved in sperm release. A physiological reduction in PACAP may therefore play a clinical role in male impotence. Outside of the CNS, the highest concentration of PACAP is found in the adrenal gland, where PACAP is the most potent stimulator of catecholamine release.

### Respiratory Organs

The major effect of PACAP in the respiratory tract is bronchodilation, an effect that is mediated primarily through the VPAC1 receptor. Expression of PAC1 in this system is unlikely.

### Gastrointestinal Tract

PACAP-containing enteric nerve fibers are present and colocalized with PAC1 in the stomach and intestine. PACAP is the major neural regulator of gastric acid secretion and may account for the observed nocturnal increase in secretion. VPAC1 receptors are expressed on the surface of the D cell, where PACAP, along with galanin, inhibits acid secretion through the release of somatostatin from the gastric D cell (Fig. 2). Another important effect of PACAP is in the regulation of intestinal motility. PACAP acts mainly to promote VPAC1 receptor-mediated relaxation. In the rat colon, PACAP stimulates apamin-sensitive $K^+$ channels, leading to relaxation. The major colonic peristaltic reflex is mediated via VIP whereas the descending relaxation phase of intestinal peristalsis appears to be regulated by PACAP through the VPAC1 receptor. Another novel effect that has been discovered is related to nitric oxide synthesis and the interplay between the hormones VIP and PACAP, although the exact mechanism has not been discovered.

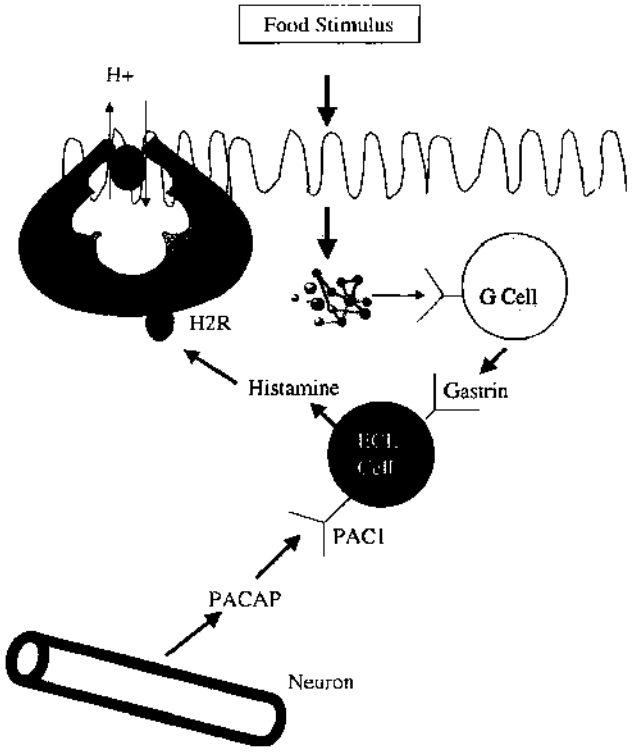


**FIGURE 2** Model for the regulation of gastric acid secretion by the hormone PACAP. Released by neurons of the gastrointestinal enteric neural plexus, PACAP binds to the PAC1 receptors of nearby enterochromaffin-like (ECL) cells. PACAP stimulation of ECL cells triggers the release of histamine. Liberated histamine then binds to histamine-2 receptors (H2R) located on the surface of stomach parietal cells, thereby regulating gastric acid secretion.

### Cardiovascular System

Similar to the respiratory system, the predominant effects of PACAP in the cardiovascular system occur through smooth muscle relaxation that is mediated through the VPAC1 receptor. In the cardiovascular system, PACAP relaxes smooth muscle through cAMP and protein kinase A, resulting in hypotension. In animals, PACAP administration results in a biphasic effect, with initial vasodilation and a later catecholamine release reflex causing an increase in blood pressure and heart rate. In cultured cardiac myocytes, PACAP exerts positive inotropic and chronotropic effects).

### Immune System

The effects of PACAP on cell-mediated immunity have not been thoroughly investigated and only recently has the expression of PAC1 been discovered on lymphocytes. In mice, PACAP stimulates murine macrophages, which in turn stimulate T cell proliferation through VPAC1 receptors, thereby releasing

interleukin-10 (IL-10) and inhibiting IL-6 and IL-12 production. VIP and PACAP inhibit IL-2 transcription in T cells by inhibiting c-Jun. VIP and PACAP have been shown to inhibit nuclear factor κB (NF-κB) by inhibiting p65 nuclear translocation and NF-κB DNA binding. In macrophages, VIP and PACAP inhibit interferon γ (IFN γ)-induced activation of the Jak1/Jak2/STAT/IRF-1 signaling cascade.

### Tumor Biology

The majority of the early work on pharmacology and signal transduction relied on tumor cells consisting of the AR42 J rat pancreatic cancer, NB-OK1, human astrocytoma, and PC-12 rat pheochromocytoma cell lines. In these cell systems, PACAP stimulates c-*fos*, c-*myc*, and c-*jun* and is a potent stimulator of cell proliferation. In human lung cancer cell lines, PACAP stimulates growth. Radioligand binding studies demonstrate expression of receptor in a large percentage of human tumors, including those of breast, prostate, pancreas, lung, colon, stomach, and liver as well as lymphomas and meningiomas.

## CONCLUSIONS

PACAP is one of the most recently described neuropeptides and therefore very little is known about its function. Its physiological relevance in health and disease is now only beginning to be understood. Recent studies of gene deletion in mice may elucidate further the functional significance of the PACAP hormone and its receptor, PAC1.

### See Also the Following Articles

**Enteroglucagon • Gastric Acid Secretion • Secretin • Vasoactive Intestinal Peptide (VIP)**

### Further Reading


Arimura, A. (1992). Pituitary adenylate cyclase-activating polypeptide (PACAP): Discovery and status of current research. *Regul. Pept.* 37, 287–303.

Delgado, M., and Ganea, D. (2000). Inhibition of IFN-gamma-induced Janus kinase-1–STAT1 activation in macrophages by VIP and PACAP. *J. Immunol.* 165, 3051–3057.

Delgado, M., and Ganea, D. (2001). Vasoactive intestinal peptide and pituitary adenylate cyclase activating polypeptide inhibit nuclear factor kappa B-dependent gene activation at multiple levels in the human monocytic cell line THP-1. *J. Biol. Chem.* 276, 369–380.

Ganea, D. (1996). Regulator effects of vasoactive intestinal peptide on cytokine production in central and peripheral lymphoid organs. *Adv. Neuroimmunol.* 6, 61–74.

Grider, J. R., and Makhlouf, G. M. (1986). Colonic peristaltic reflex: Identification of VIP as a mediator of descending relaxation. *Am. J. Physiol.* 251, G40–G45.

Harmar, A. J., Arimura, A., Gozes, I., *et al.* (1998). International Union of Pharmacology. XVIII. Nomenclature of receptors for vasoactive intestinal polypeptide and pituitary adenylate cyclase activating polypeptide. *Pharmacol. Rev.* 50, 265–270.

Koves, K., Arimura, A., Gorcs, T. G., and Somogyvari-Vigh, A. (1991). Comparative distribution of immunoreactive pituitary adenylate cyclase-activating polypeptide and vasoactive intestinal polypeptide in rat forebrain. *Neuroendocrinology* 54, 159–169.

Leyton, J., Gozes, Y., Pisegna, J. R., *et al.* (1999). PACAP (6–38) is a PACAP receptor antagonist for breast cancer cells. *Breast Cancer Res. Treat.* 56, 177–186.

Lutz, E. M., Sheward, W. J., West, K. M., *et al.* (1993). The VIP2 receptor: Molecular characterization of a cDNA encoding a novel receptor for vasoactive intestinal peptide. *FEBS Lett.* 324, 3–8.

Lyu, R.-M., Germano, P. M., Choi, J. K., Le, S., and Pisegna, J. R. (2000). The crucial amino acids within the carboxyl terminus of the PACAP receptor that are involved with signal transduction and receptor internalization: Identification of a conserved amino acid motif for members of the Class II receptor family. *J. Biol. Chem.* 275, 36134–36142.

Miampamba, M., Germano, P. M., Arli, S., Wong, H. H., Scott, D., Tache, Y., and Pisegna, J. R. (2002). Expression of pituitary adenylate cyclase-activating polypeptide and PACAP type 1 receptor in the rat gastric and colonic myenteric neurons. *Regul. Pept.* 105(3), 145–154.

Miyata, A., Arimura, A., Dahl, R. R., *et al.* (1989). Isolation of a novel 38-residue hypothalamic polypeptide which stimulates adenylate cyclase in pituitary cells. *Biochem. Biophys. Res. Commun.* 164, 567–574.

Pisegna, J. R, Leyton, J., Coelho, T., *et al.* (1997). Differential activation of immediate-early gene expression by four splice variants of the human pituitary activating polypeptide receptor: Evidence for an activation by PACAP hybrid and the phospholipase C inhibitor U73122. *Life Sci.* 61, 631–639.

Pisegna, J. R., and Wank, S. A. (1993). Molecular cloning and functional expression of the pituitary adenylate cyclase-activating polypeptide type I receptor. *Proc. Natl. Acad. Sci. U.S.A.* 90, 6345–6349.

Pisegna, J. R., and Wank, S. A. (1996). Cloning and characterization of the signal transduction of four splice variants of the human pituitary adenylate cyclase activating polypeptide receptor: Evidence for dual coupling to adenylate cyclase and phospholipase C. *J. Biol. Chem.* 271, 17267–17271.

Rawlings, S. R., and Hezareh, M. (1996). Pituitary adenylate cyclase-activating polypeptide (PACAP) and PACAP/VIP receptors: Actions on the anterior pituitary gland. *Endocrinol. Rev.* 17, 4–29.

Reubi, J. C., Laderach, U., Waser, B., Gebber, J. O., Robberecht, P., and Laissue, J. A. (2000). Vasoactive intestinal peptide/PACAP receptor subtypes in human tumors and their tissues of origin. *Cancer Res.* 60, 3105–3112.

Schworer, H., Katsoulis, S., Creutzfeldt, W., and Schmidt, W. E. (1992). Pituitary adenylate cyclase-activating polypeptide, a novel VIP-like gut-brain peptide, relaxes the guinea pig taenia caeci via apamin-sensitive potassium channels. *Naunyn Schmiedebergs Arch. Pharmacol.* 346, 511–514.

Seki, T., Shioda, S., Izumi, S., *et al.* (2000). Electron microscopic observation of PACAP-containing neurons in the rat retina. *Regul. Pept.* 21, 109–113.

Shivers, B. D., Gorcs, T. J., Gottschall, P. E., and Arimura, A. (1991). Two high affinitiy binding sites for pituitary adenylate cyclase-activating polypeptide have different tissue distributions. *Endocrinology* **128**, 3055- 3065.

Spengler, D., Waeber, C., Pantaloni, C., *et al.* (1993). Differential signal transduction by five splice variants of the PACAP receptor. *Nature* **365**, 170–175.

Vaudry, D., Gonzalez, B. J., Basille, M., *et al.* (2000). Pituitary adenylate cyclase-activating polypeptide and its receptors: From structure to functions. *Pharmacol. Rev.* **52**, 269–324.

Wang, H. Y., Jiang, X. M., and Ganea, D. J. (2000). The neuropeptides VIP and PACAP inhibit IL-2 transcription by decreasing c-Jun and increasing Jun B expression in T cells. *Neuroimmunology* **104**, 68–78.

Zeng, N., Kang, T., Wong, H., *et al.* (1999). PACAP type I receptor activation regulates ECL cells and gastric acid secretion. *J. Clin. Invest.* **104**, 1383–1391.

Zia, F., Fagarasan, M., Bitar, K., Coy, D. H., Pisegna, J. R., Wank, S. A., and Moody, T. W. (1996). PACAP receptors regulate the growth of non-small cell lung cancer cells. *Cancer Res.* **55**, 4886–4891.

# Pneumatosis, Benign and Serious

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**hematochezia** Passage of bloody stools.

**lymphangioma** Well-circumscribed nodule of lymphatic vessels; the vessels vary in size, are usually greatly dilated, and are lined with normal endothelial cells. They are most frequently found in the neck, axilla, arm, mesentery, and retroperitoneum.

**necrotizing enterocolitis** Extensive ulceration and necrosis of the ileum and colon in premature infants in the neonatal period; possibly due to perinatal intestinal ischemia and bacterial invasion.

**pneumoperitoneum** Presence of air or gas in the peritoneal cavity as a result of disease, but can also be artificially produced (i.e., postsurgical intervention).

**pseudomembranous colitis** Inflammation of the small and large bowels, with the formation and passage of pseudomembranous material in the stools usually secondary to *Clostridium difficile* toxin.

**tenesmus** Painful spasm of the anal sphincter, causing an urgent desire to evacuate the bowel or bladder and involuntary straining, with the passage of little fecal matter or urine.

**volvulus** Twisting of the intestine, causing obstruction.

**Pneumatosis intestinalis is defined as multiple submucosal, subserosal, or muscularis gas-filled cysts in the wall of the gastrointestinal tract from the stomach to the rectum. Originally, these intramural cysts were referred to as pneumatosis cystoides intestinalis, but because a linear and curvilinear distribution of the cysts also exists, the term "pneumatosis intestinalis" is now used to include all intramural gas collections. The most common locations for these cysts are, in order of prevalence, the jejunum, ileocecal region, and colon. Other structures that can be involved include the mesentery, peritoneum, and falciform ligament.**

## INTRODUCTION

Pneumatosis intestinalis (PI) is an uncommon condition that has the highest incidence in the fourth through seventh decades of life. PI is usually an unexpected finding on plain abdominal and barium radiographs and is generally a benign condition. In fact, it is the most common cause of benign pneumoperitoneum. However, when associated with fulminant conditions such as hemorrhage or intestinal necrosis, PI has serious implications. In neonates, pneumatosis is frequently associated with necrotizing enterocolitis (NEC). As a result, it is important to recognize that the prognosis of patients with PI is a function of their underlying condition and management should be based on clinical grounds.

## PATHOGENESIS

The cause of pneumatosis may be primary or secondary. The primary, or idiopathic, form is not associated with any other lesions and usually does not require

TABLE I Pulmonary Conditions Associated with Pneumatosis Intestinalis

| |
|---|
| Chronic obstructive pulmonary disease |
| Asthma |
| Cystic fibrosis (with pancreatic involvement) |
| High-pressure pulmonary ventilation |
| Chest trauma |

treatment. The secondary form has a variety of causes. The majority of cases, which are benign, are associated with chronic obstructive pulmonary disease (e.g., cystic fibrosis) or the immunocompromised state, (i.e., AIDS, high-dose steroid treatment, or chemotherapy). The more serious cases are classically related to conditions that cause bowel ischemia. A variety of related pulmonary and gastrointestinal (GI) disorders are listed in Table I and Table II. In the appropriate clinical setting, these conditions should be considered in the differential diagnosis of pneumatosis intestinalis.

The defining pathogenesis of pneumatosis is unknown, but as shown in Table III, several theories have been proposed. The proposed mechanisms can be summarized as follows:

- Primary: idiopathic cysts tend to resolve spontaneously, but can sometimes recur.
- Secondary:

A. The mucosal disruption hypothesis suggests that gas from the bowel lumen adjacent to the damaged mucosa dissects under pressure along the tissue spaces into the intestinal wall. Distant spread is thought to be through the mesentery. The mechanism for PI in collagen vascular disorders is unclear, but is likely related to vasculitis that eventually results in mucosal disruption.

B. Another mechanism suggests that the intestinal wall is penetrated by gas-forming organisms. For example, in bowel ischemia, there is microscopic infiltration of polymorphonuclear leukocytes with debris containing bacteria. Although this theory is based on strong clinical and experimental evidence, most cases of PI are not related to infection, and most cyst ruptures do not produce peritonitis.

C. Bacterial fermentation of carbohydrates may result in high intraluminal hydrogen tension. This hydrogen diffuses into the intestinal wall and attracts nitrogen, oxygen, and carbon dioxide from the blood. As a result, an intramural bubble, or cyst, is created, consisting of nitrogen as the other gases get absorbed.

D. A theory that explains the pulmonary causes of PI is the dissection of air from alveolar rupture along the bronchopulmonary bundles into the mediastinum, tracking along the major blood vessels into the retroperitoneum, and then along the mesenteric vessels to the visceral surface of the bowel.

E. Increased bowel wall permeability due to loss of structural integrity from the shrinkage of submucosal lymphoid tissue is a mechanism proposed to explain PI in immunocompromised patients.

## PATHOLOGY

Other names for PI, cystic lymphomatosis and enteromesenteric emphysema, are based on pathologic appearance. Grossly, the cysts resemble cystic lymphangiomas, hydatid cysts, or sessile polyps. A thin layer of endothelial or simple cuboidal epithelial cell lines the cysts. The diameter of the cysts can vary, if the cysts grow, from a few millimeters to a few centimeters. On cross-section, the cysts can have a

TABLE II GI Conditions Associated with Pneumatosis Intestinalis

| | |
|---|---|
| [illegible] disease | Whipple's disease |
| Intestinal obstruction | Volvulus of stomach and sigmoid colon |
| Mesenteric vascular occlusion | Intestinal lymphosarcoma, leukemia, Hodgkin's disease |
| Acute necrotizing enterocolitis | Enteric feeding via needle catheter jejunostomy |
| Chronic inflammatory bowel disease (Crohn's disease, ulcerative colitis) | Jejunoileal bypass for obesity |
| Hirschsprung's disease | Postsurgical bowel anastomosis |
| Perforated diverticulum | Abdominal trauma |
| Appendicitis | Mucosa damage from caustic agent ingestion |
| Collagen vascular disorders (scleroderma, dermatomyositis, lupus) | After sigmoidoscopy, colonoscopy, or endoscopy |
| Immunocompromised (intestinal graft-vs.-host disease, organ transplantation, bone marrow transplantation, AIDs, steroids, chemotherapy) | Biliary stent perforation |
| | Sclerotherapy |
| Cytomegalovirus infection of the intestinal mucosa | Intestinal dysmotility |
| Intestinal parasites and tuberculosis | $N_2O$ anesthesia |
| Diabetic enteropathy | Treatment with lactulose |
| | Systemic amyloidosis |

TABLE III Mechanisms of Pneumatosis Intestinalis

I. Primary
   Idiopathic
II. Secondary
   A. Mucosal disruption
      1. Increased intraluminal gas pressure
      2. Vasculitis
   B. Intestinal wall penetration by organisms
   C. Carbohydrate fermentation
   D. Retroperitoneal air dissection from lungs
   E. Decreased submucosal lymphoid tissue

"honeycomb" appearance without communication to the bowel lumen. This can be difficult to distinguish from dilated lymphatic channels, which have a similar appearance. The connective tissue surrounding the cysts usually consists of inflammatory changes. A fibrotic reaction can occur if the cysts do not spontaneously resolve, leading to their obliteration. Ultimately, this can lead to a rigid or dysfunctional intestinal wall. Puncture of these cysts during biopsy results in their collapse and sometimes a "popping" sound. Although variable, the pattern of the intramural cysts can aid in distinguishing the cause. A bubbly pattern is most common in necrotic bowel, whereas, in non-life-threatening causes the cysts are usually well localized, larger, and more spherical. They also tend to assume a linear or clusterlike pattern.

## SIGNS AND SYMPTOMS

Symptoms are nonspecific and often depend on the location of the cysts and the extent of bowel involvement, especially in the primary form. Colonic cysts are common in the primary form and can result in crampy abdominal pain, hematochezia, mucus in stools, weight loss, diarrhea, tenesmus, and flatus. Steatorrhea has been reported in idiopathic small bowel cysts, but abdominal distension and vomiting are more common when the small bowel is involved. In the secondary form, symptoms are usually related to the associated disease. Cyst rupture, usually from the small bowel, is the most common cause of nonsurgical pneumoperitoneum that is not procedure related. In healthy patients with vague abdominal complaints and free air under the diaphragm, without evidence of a perforated viscous, PI should be suspected.

In 3% of the cases, indications require immediate intervention. These include volvulus, obstruction, hemorrhage, and intestinal perforation. Peritonitis can also occur, but is unusual. When PI complicates intestinal ischemia or pseudomembranous colitis, it should be regarded as an ominous sign. In neonates, one of the serious causes of PI is NEC. These babies often present with emesis, feeding intolerance, abdominal distension, increased gastric residuals, and bloody stools. Nonetheless, the physical exam can be misleading. The presence of abdominal free air can cause the abdomen to be tympanitic. Free air between the liver and diaphragm may obscure normal liver dullness on percussion. If the cysts are large, they may present as a palpable mobile mass. Cysts in the rectal wall can even be felt as firm nodules during a rectal exam.

## DIAGNOSIS

### Adults

Upright or decubitus plain abdominal radiograph or barium studies and computed tomography (CT) usually initially suggest the diagnosis. On plain radiographs, predominantly linear or segmentally clustered intramural air is seen (see Fig. 1). The cystic pattern does not consistently correlate with the severity of PI, but the location may suggest an underlying condition or predisposing factor. In the gastric wall, linear pneumatosis should raise the question of gastric outlet obstruction or mucosal disruption from prior intubation. A mottled cystic pattern has been associated with phlegmonous gastritis. Small bowel cysts have been associated with collagen vascular diseases. Colonic cysts are common in the idiopathic form, but are also present in the setting of colitis and ischemia. The latter becomes a grave sign when associated with portal venous gas (see Fig. 2).

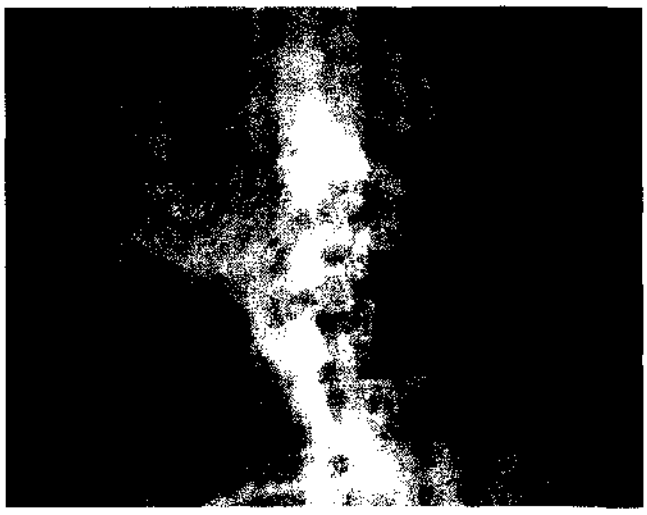

FIGURE 1 Plain frontal radiograph of the abdomen. The arrowheads point to a linear pattern of PI secondary to inflammatory bowel disease in this 22-year-old patient complaining of abdominal pain. After steroid treatment, the patient's pain resolved and she was discharged home. Radiograph courtesy of Dr. Stephen Bloom.

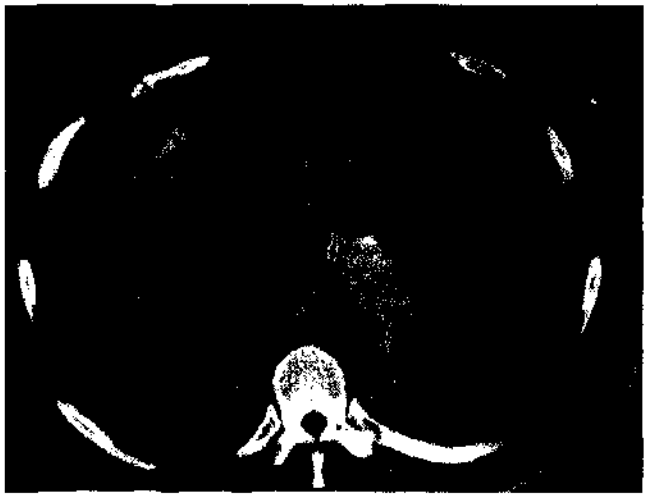

**FIGURE 2** Axial abdominal CT image without contrast. Portal venous gas is present throughout the hepatic veins in this 54-year-old female with sepsis (arrowhead). Shortly, after obtaining the CT, the patient continued to decompensate, developed shock, and then expired.

Procedures such as colonoscopy or sigmoidoscopy can result in linear colonic cysts. Air between the bowel loops may represent free air from a ruptured cyst, but a large mesenteric cyst can have a similar appearance. In the presence of isolated PI and pneumoperitoneum, idiopathic cyst rupture or ruptured pulmonary alveoli from prior general anesthesia administration should be considered. Pulmonary causes of PI also tend to be transient. On barium studies, radiolucencies indent the barium column as they line the intestinal wall, resulting in a smooth and undulating marginal pattern. CT with lung windows is probably the most sensitive tool in evaluating PI (see Fig. 3). Ultrasound (US) is another modality that can be used to make the diagnosis. On sonography, the intramural bubbles are seen as hyperechoic structures with shadowing, sometimes referred to as the "circle sign." Magnetic resonance imaging (MRI) can also aid in the diagnosis.

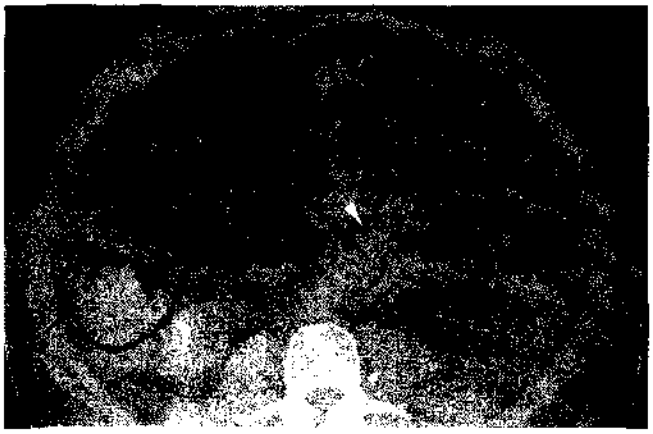

**FIGURE 3** Axial abdominal CT image with contrast. Pneumatosis is present throughout the dilated large and small bowel (arrowheads) in this 45-year-old male with ischemic bowel secondary to infection. The patient was admitted and treated with antibiotics. Clinically, the patient improved and was eventually discharged home.

## Pediatrics

NEC is a common GI emergency in neonates. The most common risk factor is prematurity. PI is present in 75% of patients with NEC and should be considered a diagnostic sign in the appropriate clinical setting. Although rare, patients with NEC can also have air in the gastric wall, known as pneumatosis gastralis, or emphysematous gastritis. No individual laboratory features are diagnostic or specific for NEC, which is why abdominal radiographs remain essential in the diagnosis and management of NEC (see Fig. 4). The presence of PI is considered a relatively early stage of NEC and can precede the clinical findings by several hours. The bubbly intramural gas collections can be confused with stool or meconium in a normal colon. Prone views or followup radiographs can help to make the distinction. In NEC, PI most commonly involves the terminal ileum and colon. It is usually associated with dilated bowel loops and an asymmetric bowel gas pattern. The cystic intramural

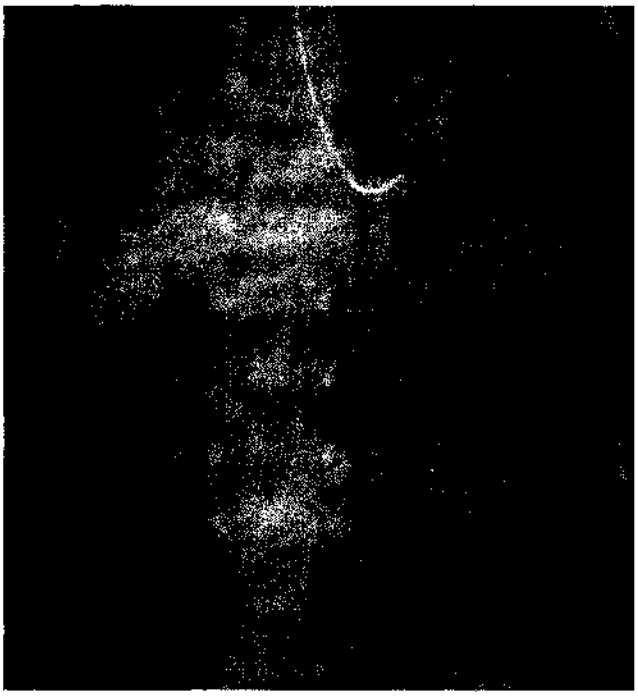

**FIGURE 4** Plain frontal radiograph of the abdomen. This premature infant presented with abdominal distension. Note the diffuse pneumatosis throughout the bowel wall. The baby was treated for NEC.

pattern may present as linear stripes, a ring, or a localized cluster. If it occurs in a more diffuse pattern, it should be a marker for a more serious condition. Ileal involvement of PI can also simulate meconium ileus. Portal venous gas is usually associated with the more severe cases of NEC and heralds surgical intervention. Sonography of the portal vein during NEC will often show bubbles of gas traveling into the liver, where they collect anteriorly, giving a characteristic echogenic loss of definition of the normal liver structure.

Colonic PI has also been associated with Hirschsprung's disease. The presence of perinatal PI should also raise the question of congenital cardiac anomalies such as hypoplastic left heart. Patients with PI who are more likely to have a poor outcome are those with underlying congenital heart disease and tissue transplants. Graft-versus-host disease, colitis, and bowel ischemia are also ominous preceding events. Contrast enemas, which are not routinely performed because of the risk of perforation, especially in NEC, show mucosal irregularity and edema. Additional causes of pediatric PI include complications of chemotherapy for leukemia and lymphoma and cardiac surgery (as listed in Table IV). The disappearance of PI or portal venous gas does not always correlate with clinical improvement. The only universally agreed indication for surgery when clinical suspicion of NEC is high is pneumoperitoneum, which is not always present in all babies with a perforation.

Several conditions may be included in the differential diagnosis of PI. However, the presence of specific secondary findings helps to differentiate PI. For example, unlike PI, enterogenous cysts are usually single. Nodules of lymphosarcoma may clinically resemble PI, but on imaging studies they are not radiolucent. The reversible thumbprint-like deformity of the mesenteric border in bowel ischemia can sometimes be misinterpreted as PI. Infectious etiologies or pseudomembranous colitis should be correlated with the clinical presentation. Mucosal polyps on barium studies result in intraluminal filling defects as opposed to the smooth, scalloped margins of PI. Crohn's colitis and ulcerative colitis also result in barium filling defects, but without cystic lucencies. It is important to realize that any of the related conditions mentioned here can be included in the differential assessment of PI, but it is the clinical setting that should guide the correct diagnosis.

**TABLE IV Pediatric Conditions Associated with Pneumatosis Instestinalis**

| |
|---|
| Necrotizing enterocolitis (usually involves the terminal ileum, colon) |
| Hirschsprung's disease |
| Congenital cardiac anomalies (i.e., hypoplastic left heart) |
| Graft-versus-host disease |
| Ischemic bowel |
| Postchemotherapy for leukemia and lymphoma |
| Postcardiac surgery |

## MANAGEMENT AND CONCLUSION

PI is generally an asymptomatic benign entity, but on rare occasions can also be serious. In the absence of intestinal inflammation or necrosis or a high white blood count, and with a benign physical exam, conservative treatment is safe. Hyperbaric oxygen to decompress the cysts and antibiotics have demonstrated some efficacy, but watchful management can be sufficient. When a life-threatening complication such as bowel perforation, obstruction, hemorrhage, or intestinal ischemia occurs in the setting of PI in the adult or pediatric population, immediate surgical intervention may be crucial to the patient's outcome.

### See Also the Following Articles

**Cystic Fibrosis • Necrotizing Enterocolitis**

### Further Reading


Buonomo, C. (1999). Neonatal imaging. *Radiol. Clin. North Am.* 37(6), 1187–1198.

Hoer, J., Truong, S., Virmich, N., Fuzesi, L., and Schumpelick, V. (1998). Pneumatosis cystoides intestinalis: Confirmation of diagnosis by endoscopic puncture, a review of pathogenesis, associated disease and therapy and a new theory of cyst formation. *Endoscopy* 30(9), 793–799.

Longo, W., Ballantyne, G., and Graham, A. (1987). Pneumatosis cystoides intestinalis. *J. Clin. Gastroenterol.* 9, 571–573.

Meyers, M., Ghahremani, G., Clements, J., and Goodman, K. (1977). Pneumatosis intestinalis. *Gastrointest. Radiol.* 2, 91–105.

Mularski, R., Sippel, J., and Osborne, M. (2000). Pneumoperitoneum: A review of nonsurgical causes. *Crit. Care Med.* 28(7), 2638–2643.

Pear, B. L. (1998). Pneumatosis intestinalis: A review. *Radiology* 207, 13–19.

Davila, A. D. and Willenbucher, R. F. (1998). Pneumatosis cystoides intestinalis. In "Sleisenger & Fordtran's Gastrointestinal and Liver Disease" (M. Feldman, B. F. Scharschmidt, and M. H. Sleisenger, eds.), 6th Ed., pp. 1979–1982. W. B. Saunders, Philadelphia.

Evers, B. M. (2001). Pneumatosis intestinalis. In "Sabiston Textbook of Surgery" (C. M. Townsend, ed.), 16th Ed., pp. 910–911. W. B. Saunders, Philadelphia.

Shimada, M., *et al.* (2001). Pneumatosis cystoides intestinalis treated with hyperbaric oxygen therapy: Usefulness of an endoscopic ultrasonic catheter probe for diagnosis. *Jpn. Med.* 40(9), 806–809.

Virginia Commonwealth University (Radiology Residents). (2001). Department of Radiology Web site. The spectrum of pneumatosis intestinalis in children. Retrieved [date] from www.radlab.vcu.edu/pneumo/pneumatosis.htm.

# Polyamines

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**antizyme** An enzyme homologue of ornithine decarboxylase capable of binding and inhibiting it.

**apoptosis** An endogenous program of cellular reactions that results in cell death without allowing toxic degradation products to be released into the cellular milieu.

**confluent** Cells in culture at high density and in contact with one another so that there are no empty spaces.

**cytoskeleton** The inner framework of the cell. It maintains and adapts cell shape, makes directed migration possible, and provides strength and organization for cellular functions.

**dimer** A molecule made up of two identical units.

**down-regulating** Reducing the level of a product by inhibiting its synthesis, degrading it, or transporting it out of the cell.

**filopodia** Narrow spike like extensions of cell borders in cells that are not necessarily migrating.

**focal adhesions** Concentrated patches of stress fibers, associated proteins, and integrin receptors on the plasma membrane by which integrins attach to the extracellular matrix.

**lamellipodia** Wide wave like extensions of the cell border in migrating cells.

**lamina propria** A layer of mostly fibroblastic cells that forms the extracellular matrix for epithelial cell attachment. It lies between the epithelium and the muscularis.

**neoplastic** Rapidly growing cells that are not necessarily transformed

**organelles** Small intracellular "organs" that perform specialized tasks.

**overexpression** Production of excessive amounts of a product by cells because extra copies of the gene encoding the product have been introduced into the cell chromosomes

**26S-proteosome** A specialized lysosome in cytoplasm that degrades discarded molecules.

**subconfluent** Cells at low density that have not yet formed a continuous layer

**transfected** Cells with artificially introduced genes in their chromosomes

**transformed** Cells with altered DNA that have lost normal regulatory control.

**villi** Finger-like projections of mucosa covered with differentiating epithelial cells that increase the absorptive area of the intestine

**Although polyamines are required in a large, but still unknown, number of the most basic functions in all forms of eukaryotic and prokaryotic life, an understanding of their participation in the life of the cell has been many years developing. With every discovery of another biological function that requires them, an entirely new interdependent set of cellular reactions previously unsuspected is found. This article attempts to describe the current knowledge of polyamines in the cellular physiology of the gastrointestinal mucosal epithelium.**

## INTRODUCTION

### A Brief History of Polyamine Discovery

During the period of the Scientific Revolution, Antonie van Leeuwenhoek, using an early microscope, began to explore the previously invisible world of various plant and animal samples. In 1678, he wrote a now famous letter to the Royal Society of London in which he reported observing sperm as well as a slowly crystallizing substance in human semen. Two hundred forty-six years later, the "slowly crystallizing" substance was identified as spermine phosphate and the letter became the earliest documented record of a polyamine.

As chemistry evolved from alchemy, the gases oxygen, carbon dioxide, and nitrogen were fractionated from air. Methods were developed for their analyses and studies of oxidized and reduced nitrogen (ammonia) followed. In 1838, F. Wohler converted ammonium cyanate to urea. His studies led to the detection of nitrogen in more complex compounds such as uric acid, allantoin, and asparagine and established organic chemistry as a new field of chemistry. Organic chemistry, in turn, revealed the structures of the amines and polyamines and resulted in the development of other branches of chemistry, i.e., analytical chemistry, pharmacology, biochemistry, microbiology, and immunology. The beer and wine industries, searching for new methods to improve fermentation and avoid spoilage, isolated and identified the basic amino acids arginine, lysine, and ornithine and other amino acids soon followed. Other key discoveries were the structural role of nitrogen, an ornithine cycle in mammalian liver, and specific amino acid decarboxylases and oxidases. Spermine, cadaverine, putrescine and spermidine were

identified in 1881, 1886, 1889, and 1927, respectively. After that, further progress toward understanding their biological functions stalled until the 1960s when biochemists began to investigate the structure of polyamines in relation to their effects on organ function, animal metabolism, and nutrition. Research on polyamines has greatly accelerated in recent years. Over the period 2001 to 2002 alone, the National Library of Medicine lists more than 1000 reports dealing with polyamines.

The authors have borrowed much of this short history of polyamines from their first observation to the period ending with World War II from a detailed timeline published as an appendix in the 1998 book *Polyamines* by Seymour S. Cohen (see Further Reading).

### The Distribution of Polyamines in Nature

Originally, biologists thought that spermine was found only in higher eukaryotes and that prokaryotes had only putrescine and spermidine. As an increasing variety of microbes, plants, and animals were investigated, many exceptions appeared. For example, in prokaryotic thermophilic microbes, nucleic acids are distorted by hydrogen bonding at the temperatures at which they live (65–75°C) and proteins can be synthesized only when the nucleic acids are bound to spermine. Some halophiles living in very-high-salt environments lack polyamines entirely. Eukaryotic photosynthetic algae, yeast, and slime molds contain putrescine and spermidine but often do not contain spermine. Spermine is absent in protozoa and shrimp but present in mollusks, arthropods, echinoderms, and tunicates. Unusual polyamines, i.e., hydroxypolyamines, branched tertiary polyamines, and quaternary polyamines, are found in prokaryotic thermophilic microbes and in some eukaryotic animals. Even more unusual are two eukaryotes, the plant *Arabidopsis thaliana* and the protozoan *Trypanosoma cruzi*, neither of which has ornithine decarboxylase (ODC), the rate-limiting enzyme that controls the biosynthesis of polyamines. Putrescine, spermidine, and spermine are present in all cells of all vertebrates.

## BIOCHEMISTRY

### Polyamine Structure

The four basic polyamines in mammals and in human are putrescine, cadaverine, spermidine, and spermine. Putrescine and cadaverine are primary diamines, 1,4-diaminobutane, and 1,5-diaminopentane, respectively. Cadaverine is usually a product of bacteria in the gut. Strictly speaking, the diamines are not polyamines, but they are often included with the polyamines for the sake of convenience. Spermidine is a triamine and spermine is a tetramine. Both contain primary and secondary amines ($R_1R_2NH$). Other natural polyamines that include tertiary ($R_3$) and quaternary ($R_4N^+OH$) amines have been found as have moieties with one carbon less than the usual 1,4-diaminobutane, called norspermidine or norspermine.

### Biosynthesis of the Polyamines

Three key enzymes, all with short half-lives, are responsible for the biosynthesis of the natural polyamines, putrescine, spermidine, and spermine (see Fig. 1). The three enzymes are ODC, S-adenosylmethionine decarboxylase (AdoMetDC), and spermidine/spermine acetyltransferase. ODC is the rate-limiting enzyme because, by decarboxylating ornithine to synthesize putrescine, it provides both an active polyamine and a precursor of other polyamines. AdoMetDC decarboxylates S-adenosyl methionine to make spermidine by transferring its aminopropyl moiety to putrescine and, by another aminopropyl transfer to spermidine, to make spermine. Spermidine/spermine acetyltransferase regulates polyamine interconversion and allows cells to adjust the levels of the three polyamines. The higher eukaryotes also have another pathway by which, with acetylation and oxidation, spermine can be converted to spermidine and spermidine to putrescine. Spermidine synthase, spermine synthase, and polyamine oxidase, an enzyme that oxidatively splits the monoacetyl derivatives of spermidine and spermine, are usually present in excess and are not rate-limiting under physiological conditions. In nontumorigenic rapidly dividing cells such as embryonal cells and gut mucosal cells, ODC synthesizes transient high levels of putrescine. In nonproliferating cells, AdoMetDC provides a basal level of putrescine by conversion from spermidine. Research on the structure of ODC has shown that it is a dimer of 52 to 55 kDa subunits and is well conserved in eukaryotes from fungi to humans. In addition, it has been crystallized and found to be a group IV pyridoxal phosphate-dependent enzyme.

## POLYAMINE REGULATION

### How Is ODC Regulated?

The response of ODC to hormones or growth factors in tissues and cultured cells is typically a rapid 10- to 100-fold increase in ODC activity followed by an equally rapid decrease even before the cells begin DNA synthesis. The speed and extent of these responses were unexpected and investigators have wondered

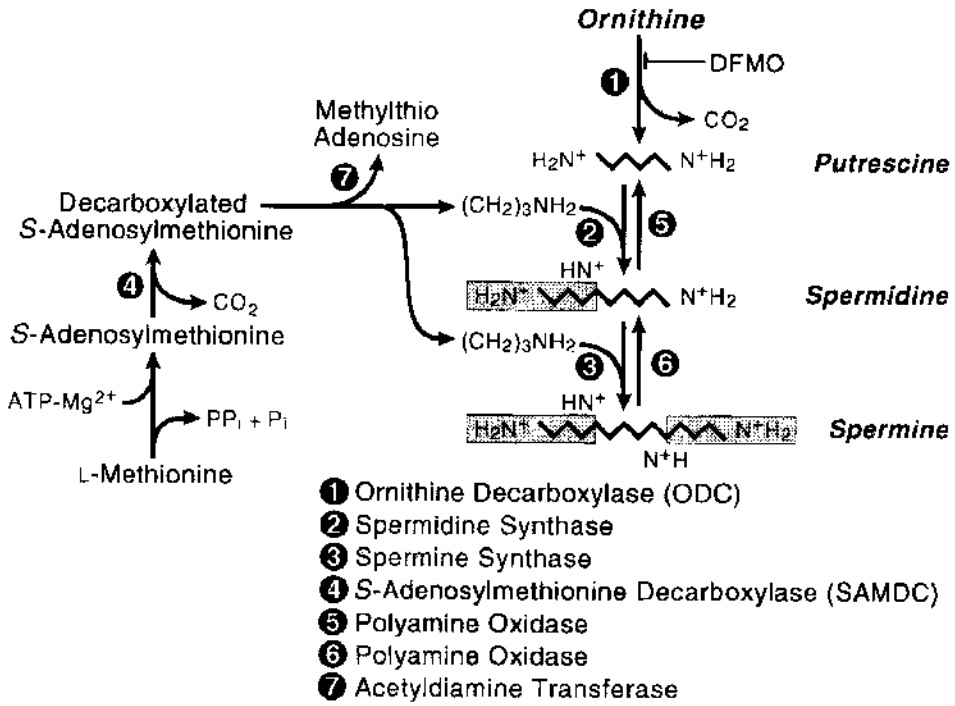



**FIGURE 1** The biosynthesis of the major physiological polyamines and their precursor, putrescine. The polyamines are shown in shorthand representation, i.e., putrescine is $H_2NCH_2CH_2CH_2CH_2NH_2$. Thus, putrescine has 4 CH groups, spermidine has 7, and spermine has 10. They carry two, three, and four positive charges that reflect the strength of their ability to bind to anions. The enzymes involved in the reactions are numbered. Reprinted from McCormack, S. A., Ray, R. M., and Johnson, L. R. (2002). Polyamines in intestinal epithelial restitution. *In* "Gastrointestinal Mucosal Repair and Experimental Therapeutics" (C.-H. Cho and J.-L. Wang, eds.), 3rd Ed., Vol. 1, pp. 43–56. Karger, Basel, Switzerland, with permission.

how the sudden decreases in ODC and polyamines are controlled especially since prolonged high levels of polyamines are toxic to cells. Several regulatory processes for the polyamines have been proposed, i.e., negative feedback and repression, antizymes, and segregation by macromolecules. Negative feedback and repression is a process common to many enzymes. In the case of ODC, negative feedback is mediated through translational expression at the 3′-untranslated region of ODC mRNA. Antizymes, analogues and suicide inhibitors of ODC, are novel endogenous ODC inhibitors. These inhibitors are unique in two respects. They target the enzyme ODC for degradation (most enzymes are targeted by ubiquitin) and they are induced by rising levels of ODC's product, spermidine. Also, in addition to down-regulating ODC, antizymes inhibit polyamine uptake and stimulate its outward transport. Finally, some investigators have suggested that negative feedback may not function in the low levels of free polyamines. Most of the polyamines produced at any one time are quickly segregated because they are strongly basic due to their amine groups and bind to proteins, DNA, RNA, and other negatively charged macromolecules. The free polyamines remaining can be regulated by antizymes. Some investigators have suggested that ODC may be regulated for the control of another as yet unknown reaction. If this should be demonstrated, it would open new and exciting possibilities for polyamine research. At present, the most obvious and only proven role of ODC is to provide a biosynthetic route for putrescine and cadaverine.

## Synthetic Inhibitors of Polyamines

The rapid rise and fall of the polyamine biosynthetic enzymes ODC and AdoMetDC intrigued biochemists when they observed it during the 1960s. When polyamines were found in large quantities in the tumors, blood, and urine of cancer patients, biochemists began to synthesize inhibitors in the hope that they could lower the levels of polyamines and stop the growth of the tumors. α-Difluoromethylornithine (DFMO) and methylglyoxal-bis-guanylhydrazone (MGBG) emerged as promising inhibitors.

DFMO is one of the most useful of the synthesized inhibitors of ODC because it irreversibly and

specifically inhibits ODC, blocks the production of putrescine from ornithine, inhibits or reduces any cell functions that require putrescine, is relatively nontoxic, and is easily dissolved in aqueous medium. Experiments with animals and cells in culture have shown that the specificity of polyamine deficiency can be demonstrated by supplying a polyamine at the same time as the DFMO because the combination can maintain any inhibited function at near normal levels. DFMO is widely used experimentally to study the effects of polyamine depletion on cell growth, migration, attachment, the actin cytoskeleton, signaling, etc., in culture and *in vivo*.

MGBG is an effective inhibitor of spermidine synthesis by AdoMetDC. However, it is more toxic than DFMO, may reduce the availability of methionine for protein synthesis, and, unexpectedly, has been shown to increase polyamines to very high levels in the brain. Both MGBG and DFMO have been used in cancer therapy and, in some cases, have caused improvement. Researchers continue to synthesize new inhibitors in the hope of improving their effectiveness. Unfortunately, reducing polyamines significantly in the gastrointestinal tract is difficult even when polyamines are severely restricted in the diet because they are contributed by food, bacteria, and sloughed cells in the lumen.

## POLYAMINE ROLES IN ESSENTIAL PHYSIOLOGICAL PROCESSES

### Cytoskeletal Maintenance

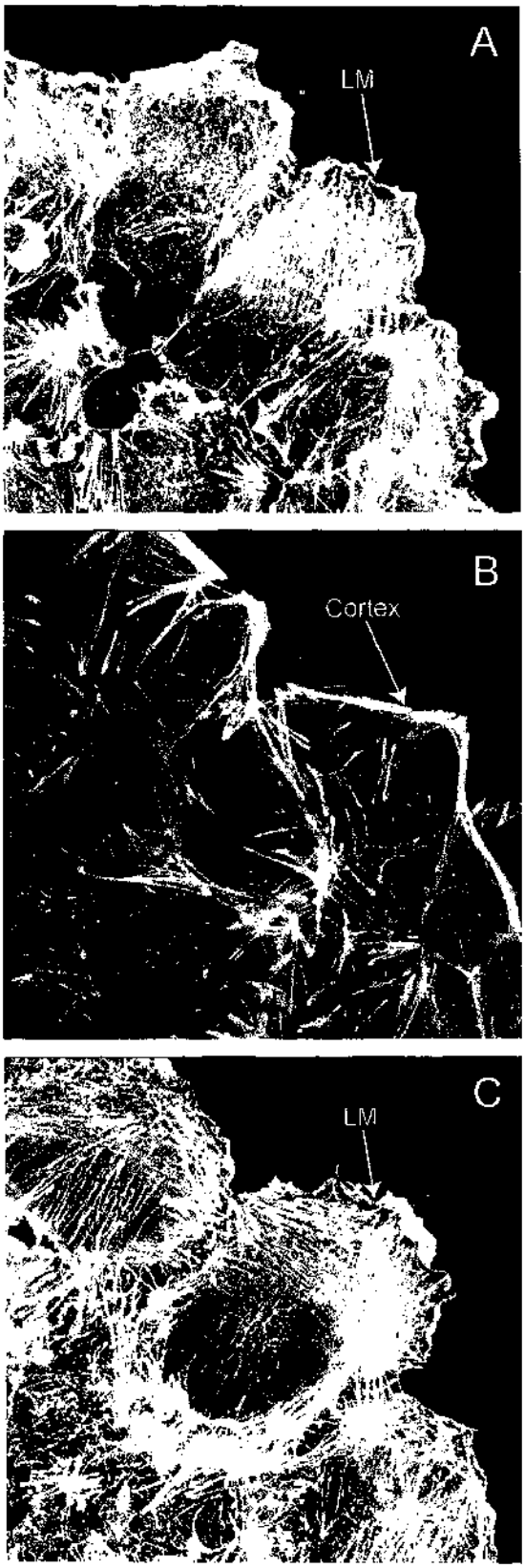
The cytoskeleton is the framework of cellular structure and organization. Actin is its major protein and is present in two forms. The filamentous form of actin, F-actin, polymerizes and depolymerizes continuously to meet the demands of the moment with the help of an array of associated proteins. In the process, F-actin provides shape, rigidity, and strength to the cell. The monomeric form, G-actin, is the result of F-actin depolymerization as well as a source of new monomers for polymerization. Nonmuscle myosin II, a second protein intimately involved with the cytoskeleton, is the motor for cytoskeletal movement. It also adjusts cell shape, responds to calcium levels, and transports and distributes organelles and proteins. Polyamine deficiency decreases nonmuscle myosin II protein by 75% and changes its distribution so that it no longer binds to actin filaments but aggregates in apparently nonfunctional clumps. Other actin-binding proteins important for cytoskeletal function are also adversely affected by polyamine deficiency.

Under the microscope, the cytoskeleton presents a beautiful, intricate pattern when stained with fluorescently linked phalloidin, a toxin of *Amanita phalloides* that binds and stabilizes polymeric actin. The effects of polyamine deficiency on the cytoskeleton can be easily recognized because the distribution of F-actin in the cell is radically altered (see Fig. 2). Actin filaments and stress fibers disappear from the cell interior and concentrate at the cortex rather than maintain their usual position throughout the cell. Even when subconfluent, the cells are rounded and have few of the extensions (lamellipodia and filopodia) seen in normal subconfluent cells. This rearrangement shows that cytoskeletal functions necessary for cell migration, such as polarization, control of direction, cell shape, signaling, and ability to generate force, are disrupted, severely disabling attachment, spreading, and migration. These phenotypic changes were first noticed over 20 years ago in cells with mutant ODC genes.

### Cell Growth

Polyamines are required for growth in almost all cells. An adequate supply of polyamines is especially important to the gastrointestinal epithelium where 72 h is the length of an average cell's life. Cell growth (as proliferation) is the basis of the continual renewal of the gastrointestinal epithelium. The epithelium lies in a single layer on the mucosa. It is not a level layer but an arrangement of pits (crypts) and their associated villi that expand the tract's absorptive surface enormously. The depth of the crypts and height of the villi vary in different parts of the tract. A single stem cell at the bottom of each crypt divides continuously; its progeny divide further and move up onto the villi, differentiating as they go into the various types of functional cells of the gastrointestinal epithelium. The oldest cells at the villous tips undergo apoptosis (a programmed death process that minimizes toxicity to surrounding cells) and are sloughed off into the lumen after approximately 72 h. The precise and timely progression of this cycle is vital to the health of the gastrointestinal tract and is dependent on polyamines.

Polyamines are supplied to the gastrointestinal epithelial mucosa from four sources, making its experimental elimination exceedingly difficult. The sources are as follows: (1) new synthesis via ODC in proliferating cells; (2) absorption of dietary polyamines, bacterial products, and intestinal secretions in the lumen; (3) absorption of polyamines from sloughed intestinal villous cells in the lumen; and (4) synthesis via ODC in villous cells transported to the crypt cells through mucosal circulation (see Fig. 3). Polyamines appear in the human gut after a meal and soon disappear from the duodenal and jejunal lumen, a consequence of




absorption and distribution to remote organs and tissues. Normal or neoplastic epithelial cells of the gut mucosa take up polyamines by an active transport process that can be stimulated by mitogens and peptide growth factors.

In culture, normal, transformed, or ODC gene-deleted mutants also depend on polyamines for growth. After the removal of supplemental polyamines from the medium of ODC gene-deleted cells or after treatment of normal cells with DFMO, proliferation is reduced nearly to zero by the time all cells have reached cell cycle stage G1. The cell cycle is arrested at G1 because of an increase in cell cycle inhibitors p21, p27, and p53. Without ODC, the pool of putrescine rapidly falls to very low levels and the source of putrescine from which AdoMetDC synthesizes spermidine is no longer available either. The spermine pool does not fall lower than 40% of normal, probably because it is largely bound to macromolecules. Conversely, cells transfected to overexpress the ODC gene do not require supplemental polyamines and DFMO can depress their growth only marginally.

## Cell Migration

When damage to the gastrointestinal epithelial tract occurs, it must be repaired quickly in order to maintain a barrier to the spread of infection throughout the body. Repair occurs in two stages. The first, restitution, can last up to 12 h and consists of a response to cytokines, hormones, and factors secreted by surrounding cells. The restitution response in gastrointestinal epithelial cells consists of extending the cytoplasm in lamellipodia and filopodia into the wounded area. These specialized structures attach to the extracellular matrix through focal adhesions that form on their leading edge. Focal adhesions at the rear of the cell detach, allowing the trailing end of the cell to be drawn up. The process is

FIGURE 2 The migrating edge of rat intestinal cells (IEC-6) in culture. The cells are shown at 3 h of migration after 4 days of (A) no treatment (control), (B) DFMO, or (C) DFMO plus putrescine. F-actin is stained with Texas red phalloidin. The abundance of F-actin is obvious in the control and DFMO plus putrescine groups. Cell polarization toward the open area and lamellipodia (LM) are also plainly visible. The DFMO group shows scarce interior stress fibers, a thickened cell cortex (cortex), and the lack of lamellipodia characteristic of polyamine deficiency. Reprinted from McCormack, S. A., Ray, R. M., and Johnson, L. R. (2002). Polyamines in intestinal epithelial restitution. *In* "Gastrointestinal Mucosal Repair and Experimental Therapeutics" (C.-C. Cho and J.-L. Wang, eds.), 3rd Ed., Vol. 1, pp. 43–56. Karger, Basel, Switzerland, with permission.

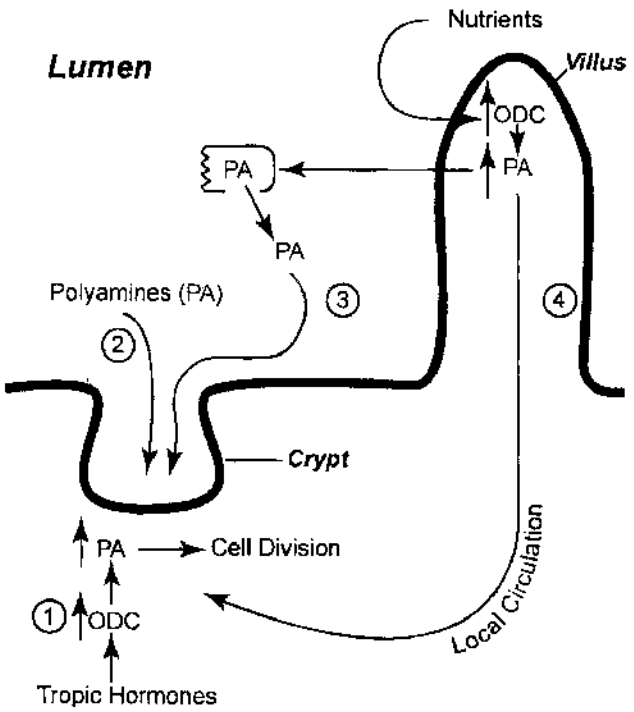



**FIGURE 3** Model depicting how polyamines from various sources could reach the proliferating cells of the intestinal crypt and influence growth. The model reconciles the effects of various lumenal stimulators and hormones with known changes in mucosal growth. The numbers refer to four different mechanisms by which polyamines reach proliferating cells: (1) new synthesis via the ODC within the proliferating cell; (2) absorption from the lumen of polyamines supplied by the diet, intestinal secretions, or bacterial synthesis; (3) absorption from the lumen of polyamines contained within sloughed villous cells; and (4) synthesis via ODC in villous cells and transportation to the crypt cells in the mucosal circulation. Reprinted from Johnson, L. R., Tseng, C.-C., Wang, P., Tipnis, U. R., and Haddox, M. K. (1989). Mucosal ornithine decarboxylase in the small intestine: localization and stimulation. *Am. J. Physiol.* 256 (*Gastrointest. Liver Physiol.* 19), G624–G630, with permission.

repeated to cover as much of the wound as possible. In other words, restitution is primarily a function of spreading and migration. After 12 h, the second stage of repair begins with the advent of cell proliferation. Hormones and growth factors play an important role during this stage as well. Growth continues until the wounded area is again covered with epithelium as before.

The severe inhibiting effects of polyamine deficiency on cell migration have been known since the early 1990s. Gastrointestinal mucosal wounds heal slowly in polyamine-deficient animals. Cultured cells from intestinal and gastric cells as well as cells from a variety of tissues show greatly reduced migration in quantitative migration studies. Investigators have found that this reduction is due to a number of specific effects that impinge on cell migration. These include rearrangement of the actin cytoskeleton, reduced focal adhesion signaling, impaired attachment, reduction of RhoA activity, reduced phosphorylation of specific transcription factors, and other cytoskeletal damaging effects. These observations open the door to undiscovered functions of the polyamines.

Since restitution primarily relies on the machinery of migration, it is heavily dependent on polyamines. Not only is it important to reinstate the barrier to microorganisms in the gastrointestinal tract quickly if it is breached, but the success of the second stage of repair depends to some extent on the success of the first.

The deceptively simple process of extending the cell's border into lamellipodia deserves some explanation in order to appreciate at least part of the elaborate mechanism involved. The lamellipodia have dense, branching actin filaments formed by the activity of the Arp2/3 complex at their outer leading edge. As more actin filaments form near the leading edge, the cell membrane is pushed outward. Focal adhesion sites form on the outer membrane through which integrin receptors can bind to ligands in the extracellular matrix. The key players coordinating this integrated system are the Rho family of small GTPases, specifically RhoA, Rac1, and Cdc42. RhoA regulates the assembly of actin stress fibers, focal adhesions, and contractility. Rac1 stimulates actin polymerization and the formation of ruffles and Cdc42 controls the formation of filopodia. New investigations show that the Rho family proteins have many other molecular links to the actin cytoskeleton through which they regulate actin polymerization, depolymerization, the activity of actin myosins, the speed of migration, and other processes.

## ARE POLYAMINES INVOLVED IN GASTROINTESTINAL DISEASE?

### Cancer

High levels of ODC activity and intracellular polyamines are common in cancer tissue. In premalignant tissue, they are a reliable sign of increased proliferation rates. Therefore, extracellular fluid polyamine levels that reflect intracellular events can be useful indicators of the effectiveness of therapy. For instance, in Barrett's-associated adenocarcinoma of the esophagus, an increase in tissue polyamine levels has been used to detect the disease still in an occult stage. In colon cancer patients on a low-polyamine diet, polyamine levels in urine may be useful for evaluating the effectiveness

of therapy. DFMO and MGBG have been effective treatments in some cases of colon cancer. Polyamine analogues that inhibit polyamine metabolism are also a possible adjunct to chemotherapy.

### Gastrointestinal Immune System Diseases

The mucosal immune system is the first line of defense against microbial and dietary antigens. It connects closely regulated inductive (Peyer's patches) and effector (lamina propria) tissues for the induction of the immune (IgA) response sites that maintain immunological homeostasis in the gut. If homeostasis is lost, inflammatory bowel disease, Crohn's disease, colitis, gastric ulcer, cancer, celiac disease, and other gastrointestinal problems can result. Approximately 50% of the population is infected with *Helicobacter pylori*, bacteria responsible for most cases of peptic ulcer. These bacteria elicit a strong inflammatory response that becomes chronic and, instead of providing protection, eventually contributes to tissue damage and ulcer. Fortunately, the disease develops only in people with a specific combination of bacterial, environmental, and genetic factors. The polyamine content of the lumen is essential for normal healing in peptic and intestinal ulcer. Polyamines can protect cells against apoptosis in growth situations, but when normal cellular regulatory functions are lost, they can also encourage apoptosis in cells that are part of the immune defense system. Inhibitors of polyamine biosynthesis, polyamine analogues, and combinations of polyamine analogues with oligonucleotides may also be candidates for prevention and treatment in these diseases.

### Aging

Polyamines are implicated in several changes that accompany aging in humans. One of these is increased susceptibility to gastrointestinal mucosal damage. The gastric mucosa is especially subject to mechanical and chemical damage, bacterial attack, ischemic damage, aberrant immunological responses, and stress. These types of damage must be repaired promptly by restitution and proliferation to avoid impairment of mucosal function. The gastrointestinal mucosa is dependent on epidermal growth factor and other hormones to maintain growth and cell differentiation as cells advance from the crypts onto the villi. With aging, polyamine levels, prostaglandins, cyclooxygenases, and epidermal growth factor receptors are decreased. The sum of these age-related changes retards restitution, cell migration, and proliferation and seriously impedes the repair of gastrointestinal mucosal damage.

### Intestinal Parasites

Two billion people in developing countries are seriously debilitated by intestinal parasites. Yet, investigation of polyamines in these parasites was begun only in the past 10–15 years. More detailed knowledge on a variety of parasites is essential to prevent and cure these diseases.

All helminthic parasites that have been studied contain spermine and spermidine but lack significant amounts of putrescine. They also do not have ornithine, arginine, or S-adenosylmethionine decarboxylases and, therefore, their survival and growth are not affected by ODC or AdoMetDC inhibitors. Apparently they cannot biosynthesize polyamines and must depend on uptake from the lumen of their hosts. This fact offers a unique and convenient treatment modality. Depending on the parasite, a polyamine-free diet or the inhibition of polyamine transport may be an effective treatment. Other helminthic parasites have unusual polyamine homologues, a degradative pathway operating through N-acetyl polyamines, possibly a new type of ODC, etc. The fact that some parasites must obtain necessary polyamines in unusual ways may offer effective and specific treatments that could be utilized to a greater degree than at present.

## SUMMARY

The history of the polyamines throughout the development of the biological sciences is a fascinating story. Biologists have been slow to appreciate the roles polyamines play in physiological processes, perhaps because there are so many roles and also for lack of necessary tools. The distribution of polyamines in nature is more varied and individual than was expected. All vertebrate mammals do have the same three natural polyamines, putrescine, spermine, and spermidine, and they synthesize, transport, interconvert, and degrade them by similar pathways. Although all of the facts about polyamine regulation are not yet at hand, it is clear that they can be toxic and that regulation is necessary. The association between rapid cell proliferation, polyamine levels, and cancer stimulated a search for synthetic polyamine inhibitors that is still ongoing in pharmaceutical laboratories. Inhibitors for both polyamine biosynthetic pathways are now available. DFMO and MGBG are especially useful in cell culture studies though less successful in treating human cancer. Recently, experiments using deletion and transfection of the ODC gene have corroborated the effects of DFMO. Polyamines are essential for cell proliferation, differentiation, migration, signaling, and attachment.

The cytoskeleton requires polyamines for virtually all of its normal functions. Repair of the gastrointestinal mucosa requires polyamines for the coordination of restitution and proliferation. Finally, polyamines are important in human gastrointestinal diseases, both from the standpoint of excess and of deficiency. Cancer, immune diseases, and diseases of aging can all result from failure to maintain polyamines at normal levels. Finally, polyamines may underlie other essential processes that have not yet been discovered. In short, continued vigorous investigation of polyamines promises to benefit both medical and basic science.

## Acknowledgment

This work was supported by Grants DK16505 and DK52874 from the National Institutes of Health.

## See Also the Following Articles

**Epithelium, Proliferation of • Epithelium, Repair of**

## Further Reading

Brabender, J., Lord, R., Danenberg, K., Metzger, R., Schneider, P., Uetake, H., Kawakami, K., Park, J., Salonga, D., Peters, J., DeMeester, T., Holscher, A., and Danenberg, P. (2001). Upregulation of ornithine decarboxylase mRNA expression in Barrett's esophagus and Barrett's-associated adenocarcinoma. *J. Gastrointest. Surg.* **5**, 174–182.

Brzozowski, T., Konturek, P. C., Konturek, S. J., Schuppan, D., Drozdowicz, D., Kwiecien, S., Majka, J., Nakamura, T., and Hahn, E. (2001). Effect of local application of growth factors on gastric ulcer healing and mucosal expression of cyclooxygenase-1 and -2. *Digestion* **64**, 15–29.

Coffino, P. (2001). Antizyme, a mediator of ubiquitin-independent proteasomal degradation. *Biochimie* **83**, 319–323.

Cohen, S. S. (1998). "A Guide to the Polyamines." Oxford University Press, New York.

Davis, R. H., Morris, D. R., and Coffino, P. (1992). Sequestered end products and enzyme regulation: The case of ornithine decarboxylase. *Microbiol. Rev.* **56**, 280–290.

Deloyer, P., Peulen, O., and Dandrifosse, G. (2001). Dietary polyamines and non-neoplastic growth and disease. *Eur. J. Gastroenterol. Hepatol.* **13**, 1027–1032.

Ernst, P. B., Takaishi, H., and Crowe, S. E. (2001). *Helicobacter pylori* infection as a model for gastrointestinal immunity and chronic inflammatory diseases. *Digest. Dis.* **19**, 104–111.

Halter, F., Tarnawski, A. S., Schmassmann, A., and Peskar, B. M. (2001). Cyclooxygenase 2—Implications on maintenance of gastric mucosal integrity and ulcer healing: Controversial issues and perspectives. *Gut* **49**, 443–453.

Johnson, R. L., and McCormack, S. A. (1994). Regulation of gastrointestinal mucosal growth. *In* "Physiology of the Gastrointestinal Tract" (L. R. Johnson, ed.), 3rd Ed., Vol. 1, pp. 611–641. Raven Press, Washington, DC.

Kiyono, H., Kweon, M. N., Hiroi, T., and Takahashi, I. (2001). The mucosal immune system: From specialized immune defense to inflammation and allergy. *Acta Odontol. Scand.* **59**, 145–153.

McCormack, S., and Johnson, L. (2001). Polyamines and cell migration. *J. Physiol. Pharmacol.* **52**, 327–349.

McCormack, S., Ray, R., and Johnson, L. (2002). Polyamines in intestinal epithelial restitution. *In* "Gastrointestinal Mucosal Repair and Experimental Therapeutics" (C.-H. Cho, J.-Y. Wang, eds.), 3rd Ed., Vol. 1, pp. 43–56. Karger, Basel.

Pollard, T. D., Blanchoin, L., and Mullins, R. D. (2000). Molecular mechanisms controlling actin filament dynamics in nonmuscle cells. *Annu. Rev. Biophys. Biomol. Struct.* **29**, 545–576.

Ridley, A. J. (2001). Rho GTPases and cell migration. *J. Cell Sci.* **114**, 2713–2722.

Robertson, D. J., and Grimm, I. S. (2001). Inflammatory bowel disease in the elderly. *Gastroenterol. Clin. North Am.* **30**, 409–426.

Silen, W. (1987). Gastric mucosal defense and repair. *In* "Physiology of the Gastrointestinal Tract" (L. R. Johnson, ed.), 3rd Ed., Vol. 1, pp. 1055–1069. Raven, New York.

Thomas, T., and Thomas, T. J. (2001). Polyamines in cell growth and cell death: Molecular mechanisms and therapeutic applications. *Cell. Mol. Life Sci.* **58**, 244–258.

Wallace, H. M., and Caslake, R. (2001). Polyamines and colon cancer. *Eur. J. Gastroenterol. Hepatol.* **13**, 1033–1039.

# Porcelain Gallbladder

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**carcinoma** Any cancer that arises from the epithelium.
**cholecystectomy** Surgical removal of the gallbladder.
**cholelithiasis** The formation of stones in the gallbladder.
**hyperechoic** Ultrasound description of lesions that reflect sound waves.

**Porcelain gallbladder is a rare condition and is defined as intramural calcification of the gallbladder. Patients are generally asymptomatic and diagnosis is usually incidental. The pathogenesis remains unknown but is highly associated with cholelithiasis. Ultrasound and computed tomography are used to assist in diagnosis. There is a high incidence of gallbladder carcinoma in patients with this condition and therefore cholecystectomy is recommended. However, some recent studies show controversial results and definitive management remains to be determined.**

## INTRODUCTION

Porcelain gallbladder is a rare disease; Grandchamps first described it in 1797 and Florcken first used the term in 1929. Many terms have been used to describe the appearance of this gallbladder condition: "calcifying cholecystitis," "china gallbladder," "cholecystopathy chronic calcanea," "calcified gallbladder," and "porcelain gallbladder." The term porcelain gallbladder describes the brittle consistency and bluish discoloration of the gallbladder wall.

## INCIDENCE

The incidence is low, ranging between 0.06 and 0.8% of cholecystectomy specimens. The disease is five times more common in women between the ages of 38 and 70 years (with a mean of 54 years) than in the general population. Rarely, pediatric cases are reported.

## PATHOGENESIS

The pathogenesis of the calcification remains controversial. It occurs either as a broad, continuous band in the muscularis or as multiple punctate areas in both the glandular spaces and sinuses. Three potential mechanisms are proposed. One mechanism may be cystic duct obstruction that leads to mucosal deposition of calcium carbonate salts, resulting in bile stagnation within the gallbladder. Another mechanism of injury may be related to chronic irritation of the wall by stones or another foreign body. This theory is supported by the observation that more than 95% of patients with porcelain gallbladder also have stones. The third mechanism may be related to a dystrophic process due to chronic low-grade infection and compromised circulation from cystic duct obstruction. This process results in hemorrhage, scarring, and hyalinization of the wall, which in turn provides a matrix for the deposition of lime salts.

## CLINICAL PRESENTATION

Most patients are asymptomatic and the lesion is generally detected incidentally.

## DIAGNOSIS

Plain film usually shows a large solitary calcified mass in the right upper quadrant. However, computed tomography and ultrasound are the usual imaging modalities that provide more definitive diagnosis of porcelain gallbladder. In 1984, Kane reported three distinct sonographic patterns in nine patients. The type I pattern was identified by a hyperechoic semilunar structure with a posterior shadow and no gallstones. Type II had a biconvex, curvilinear echogenic structure with acoustic shadowing and stones, and type III had irregular echoes with posterior shadowing. In 1989, Shimizu and co-workers reviewed 30 cases in the world's literature in which ultrasound features of porcelain gallbladder were described. They recommended a simple classification: complete (complete replacement of the mucosa with dense connective tissue and calcification, correlated to type I) and incomplete (some mucosa remaining, correlated to types II and III). They found no gallstone and no cancer in the complete type. However, in the incomplete type, gallstones are detected and there is a 41% incidence of cancer. They

 

hypothesized that malignancies arise only from the mucosal epithelium and therefore gallbladder malignancy is improbable in the type I complete group.

## MANAGEMENT AND RELATIONSHIP TO GALLBLADDER CARCINOMA

Prophylactic cholecyctectomy is generally recommended due to the risk of malignancy. The incidence reported in the older literature varies from 12.5 to 61%. However, a recent study by Hines that reviewed 10,741 cholecystectomy specimens showed no carcinoma among 15 patients with porcelain gallbladder. Another study by Berger and colleagues that reviewed 25,900 gallbladder specimens confirmed the association between gallbladder carcinoma and calcified gallbladder but at a lower rate than previously estimated. The incidence of cancer depends on the pattern of calcification; selective mucosal calcification poses a significant risk of cancer (7%), whereas diffuse intramural calcification does not. Therefore, management of asymptomatic patients with debilitating comorbidities remains controversial. The natural history of porcelain gallbladder remains to be elucidated.

### See Also the Following Articles

Cholecystectomy • Computed Tomography (CT) • Gallbladder Cancer • Gallstones, Pathophysiology of • Ultrasonography

### Further Reading

Ashur, H. (1978). Calcified gallbladder. *Arch. Surg.* 113, 594–596.
Berger, D. (2001). Carcinoma in the porcelain gallbladder: A relationship revisited. *Surgery* 129, 699–703.
Hines, O. (2001). Porcelain gallbladder is not associated with gallbladder carcinoma. *Am. Surgeon* 67, 7–10.
Horton, J. (1993). Gallstone disease and its complications. *In* "Gastrointestinal and Liver Disease" (M. Sleisenger, and B. Scharschmidt, eds.), 6th Ed., Vol. 1, pp. 948–970.
Kang, R. (1984). Porcelain gallbladder: Ultrasound and CT appearance. *Radiology* 152, 137–141.
Levin, B. (1999). Gallbladder carcinoma. *Ann. Oncol.* 10, 129–130.
Shimizu, M. (1989). Porcelain gallbladder: Relation between its type by ultrasound and incidence of cancer. *J. Clin. Gastroenterol.* 11, 471–476.

# Porphyria

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genetic heterogeneity Several different mutations in the same gene are found in a genetic disorder.
porphyrin Compound with a chemical structure consisting of four pyrrole groups linked by methene bridges; the compound is pigmented and exhibits red fluorescence when exposed to ultraviolet light around 400 nm (Soret band).
porphyrinogen Reduced form of the porphyrin; not pigmented and does not exhibit fluorescence.
porphyrin precursors Early intermediates of the heme biosynthetic pathway (δ-aminolevulinic acid and porphobilinogen) from which pyrrole groups are formed.

**The porphyrias are genetic/metabolic disorders that are characterized biochemically by the excessive accumulation and excretion of porphyrins and porphyrin precursors. These compounds are intermediates of the heme biosynthetic pathway, and each of the porphyrias is associated with deficient activity of a specific enzyme in the pathway. The major clinical manifestations—photocutaneous lesions, neuropsychiatric dysfunction, and structural liver disease—are linked to the biochemical abnormalities. Therapy is directed to ameliorate the biochemical abnormalities, which improves the clinical status of patients.**

## INTRODUCTION

The first descriptions of the porphyrias appeared in the latter part of the nineteenth century. During the twentieth century, the individual porphyrias were

identified and their biochemical and clinical features were defined. The porphyrias have been classified as hepatic or erythropoietic, depending on which tissue is the major site of expression of the biochemical abnormalities. Some are also classified as acute or inducible because they are associated with episodic attacks of neuropsychiatric dysfunction. In this article, the biochemical and clinical features of the eight types of porphyria are outlined. Two conditions that may be confused with the porphyrias, secondary porphyrinuria and pseudoporphyria, are also described.

## BIOCHEMICAL ABNORMALITIES IN PORPHYRIAS

Porphyrins/porphyrinogens and porphyrin precursors are intermediates of the heme biosynthetic pathway, a critical metabolic process that involves eight enzymes. The first step in the pathway, which is the condensation of succinyl coenzyme A and glycine to form δ-aminolevulinic acid (ALA), is catalyzed by the mitochondrial enzyme ALA synthase and is rate limiting in the liver. The last step, in which ferrous iron is inserted into protoporphyrin to produce heme, also takes place in the mitochondria. Intermediate steps to form porphobilinogen (PBG) and porphyrinogens occur in the cytoplasm.

Deficient activity of an enzyme in the pathway causes a specific pattern of accumulation and excretion of porphyrins and porphyrin precursors (Table I). In the acute porphyrias, this is exacerbated during an attack due to a marked increase in hepatic ALA synthase activity. The pattern of biochemical abnormalities is used to diagnose porphyria in a patient with compatible clinical features. Demonstration of deficient enzyme activity in cells/tissue is also used in diagnosis, particularly in acute intermittent porphyria and the familial form of porphyria cutanea tarda.

The cloning and sequencing of cDNA and genomic DNA for enzymes of the pathway have made it possible to identify gene mutations that underlie the enzyme defects in the porphyrias. Genetic heterogeneity has been found in each. Thus, molecular analysis has not yet found widespread use in diagnosis, but it is helpful in identifying asymptomatic carriers of the gene defect in families in whom a mutation has been found and for evaluating individuals in geographic areas where a specific mutation has a high prevalence. There is not usually a clear relationship between specific gene mutations and the severity of clinical and biochemical manifestations, and expression of the disease is variable even among members of a

TABLE I Biochemical Abnormalities in the Porphyrias[a]

| Type of porphyria | Enzyme defect | Location/ biosynthetic step | Major site of expression | Principal biochemical features |
|---|---|---|---|---|
| ALA dehydrase deficiency | ALA dehydrase | Cytoplasm/2 | Liver | ↑ ALA in urine |
| Acute intermittent porphyria | PBG deaminase | Cytoplasm/3 | Liver | ↑ ALA and PBG in urine |
| Hereditary coproporphyria | Coproporphyrinogen oxidase | Mitochondria/6 | Liver | ↑ ALA, PBG, coproporphyrin in urine<br>↑ Coproporphyrin in feces |
| Variegate porphyria | Protoporphyrinogen oxidase | Mitochondria/7 | Liver | ↑ ALA, PBG, coproporphyrin in urine<br>↑ Protoporphyrin in feces |
| Porphyria cutanea tarda | Uroporphyrinogen decarboxylase | Cytoplasm/5 | Liver and bone marrow | ↑ Uroporphyrin in urine<br>Isocoproporphyrin in feces |
| Hepatoerythropoietic porphyria | Uroporphyrinogen decarboxylase | Cytoplasm/5 | Liver | ↑ Zn-protoporphyrin in red cells<br>↑ Uroporphyrin in urine<br>Isocoproporphyrin in feces |
| Erythropoietic porphyria | Uroporphyrinogen III synthase | Cytoplasm/4 | Bone marrow | ↑ Uroporphyrin in red cells<br>↑ Uroporphyrin in urine |
| Erythropoietic protoporphyria | Ferrochelatase | Mitochondria/8 | Bone marrow (liver variable) | ↑ Protoporphyrin in red cells<br>↑ Protoporphyrin in feces |

[a] Abbreviations: ALA, δ-aminolevulinic acid; PBG, porphobilinogen.

family. Thus, other genetic and/or acquired factors are often critical to the phenotypic expression of the disorder.

## HEPATIC PORPHYRIAS

Several porphyrias are classified as hepatic because the liver is the major site of expression of the biochemical abnormalities (Table I). Four of the hepatic porphyrias are also termed acute because there occur episodes of severe neuropsychiatric dysfunction that are separated by asymptomatic periods (Table II). The acute attacks are precipitated by ingestion of drugs, fasting, alcoholism, infection, and hormonal effects. The most common symptom is abdominal pain, which may be accompanied by hypertension and tachycardia as manifestations of autonomic nerve dysfunction. Peripheral neuropathy causes paralysis and respiratory compromise if the attack is severe. Psychiatric manifestations include hysteria, psychosis, and depression, which sometimes persist after the attack has subsided. Seizures also occur and present a difficult problem because most antiepileptic drugs can exacerbate the attack.

During an acute attack, urinary excretion of the porphyrin precursors ALA and PBG increases markedly. Clinical and basic studies indicate that ALA may cause the neurological dysfunction. An alternate possibility is that heme deficiency in nerve tissue is the cause. Finally, both (and other) factors may underlie the attack.

Therapy of the acute attack consists of stopping the precipitating factor, carefully managing fluid and electrolyte status, and providing adequate caloric intake that is high in carbohydrates. Intravenous administration of hematin (ferriheme hydroxide) has become standard, because this may promptly ameliorate biochemical and clinical manifestations. During asymptomatic periods, patients should not take drugs that precipitate attacks, should avoid fasting and excess intake of alcohol, and should have infections treated promptly.

In four of the hepatic porphyrias, photocutaneous lesions occur (Table II). Skin fragility develops as a consequence of the photoactive properties of porphyrins deposited in skin tissue and/or circulating in dermal blood vessels. This causes blisters to form after minor trauma to sun-exposed areas. Erosions, scarring, pigment changes, and small white papules called milia subsequently develop. Sclerodermoid changes of the skin may occur in long-standing untreated disease.

In porphyria cutanea tarda, hepatic iron overload is frequent, and there is an increased prevalence of mutations in the *HFE* gene, which is associated with hereditary hemochromatosis. Patients also have a higher rate of chronic hepatitis C. In long-standing untreated porphyria cutanea tarda, there is an increased incidence of hepatocellular carcinoma. This is also found in the acute porphyrias, particularly acute intermittent porphyria, the reason for which is unclear.

The photocutaneous lesions in porphyria cutanea tarda are managed by phlebotomy to deplete excess hepatic iron, as uroporphyrin formation decreases concomitantly. Removal of 4–8 liters of blood usually resolves the clinical and biochemical abnormalities. Chloroquine or related compounds are used if phlebotomy is not tolerated. Once in remission, most patients with porphyria cutanea tarda remain free of photocutaneous lesions provided that they avoid taking iron-containing compounds and remain abstinent from alcohol. Photocutaneous lesions in variegate porphyria and hereditary coproporphyria do not respond to phlebotomy, however.

**TABLE II Clinical Features in the Porphyrias**

| Type of porphyria | Usual inheritance[a] | Usual onset of disease | Photocutaneous lesions | Neuropsychiatric symptoms | Chronic liver disease | Hepatoma |
|---|---|---|---|---|---|---|
| ALA dehydrase deficiency | AR | Childhood | − | + | − | − |
| Acute intermittent porphyria | AD | Early adulthood | − | + | − | + |
| Hereditary coproporphyria | AD | Early adulthood | + | + | − | + |
| Variegate porphyria | AD | Early adulthood | + | + | − | + |
| Porphyria cutanea tarda | AD (familial type) | Adulthood | + | − | + | + |
| Hepatoerythropoietic porphyria | AR | Childhood | + | − | + | − |
| Erythropoietic porphyria | AR | Infancy | + | − | − | − |
| Erythropoietic protoporphyria | Triallelic | Childhood | + | + (cholestatic crisis) | + | − |

[a] Abbreviations: AR, autosomal recessive; AD, autosomal dominant.

## ERYTHROPOIETIC PORPHYRIAS

In two porphyrias, erythropoietic protoporphyria (EPP) and congenital erythropoietic porphyria, the bone marrow is the major site of expression of the biochemical abnormalities. The major clinical manifestation in EPP is lifelong photosensitivity. In contrast to the other porphyrias, photosensitivity occurs acutely during sun exposure. Erythema and edema of the skin develop but blisters and erosions are rare. Chronic skin changes involve thickening and lichenification of the skin on the nose and dorsal aspects of the hands. Oral administration of β-carotene reduces photosensitivity in many patients. In some cases, the only effective management is use of opaque sunscreens or avoidance of sun exposure, even through window glass.

Hepatobiliary disease is another feature of EPP, and in approximately 5% of individuals, the occurrence of structural damage to the liver may cause liver failure and necessitate liver transplantation. Liver damage is due to the toxic effect of protoporphyrin on liver function and structure, particularly when there is progressive accumulation of protoporphyrin in the liver due to impaired excretion of protoporphyrin in bile. Therapies for this condition involve interruption of the enterohepatic circulation of protoporphyrin by using cholestyramine or activated charcoal and decreasing the excess production of protoporphyrin and improving liver function through the intravenous administration of hematin. However, when liver damage is advanced, liver transplantation is the only effective treatment. Unfortunately, disease frequently recurs in the graft because excessive production of protoporphyrin in the bone marrow is not significantly changed by liver transplantation.

Erythropoietic porphyria is a recessive disorder that usually has onset in infancy. A few cases of adult onset have been reported. Skin lesions are similar to those in porphyria cutanea tarda. As patients age, there may be progressive destruction of the fingertips, ears, and nose. Hemolytic anemia and splenomegaly are common. Therapy is generally supportive, consisting of protection from sun exposure and prompt treatment of skin infections. Red blood cell transfusion and intravenous administration of hematin are used to decrease the production of porphyrin. Splenectomy effects remission of disease in some patients.

## SECONDARY PORPHYRINURIA AND PSEUDOPORPHYRIA

Several diseases are associated with an increase in the urinary excretion of porphyrin, particularly coproporphyrin excretion, which is termed secondary porphyrinuria. These diseases include various types of anemia and malignancy, hepatobiliary diseases, diabetes, and infections. Some patients have abdominal pain and other symptoms of acute porphyria. However, with the exception of lead poisoning and hereditary tyrosinemia, urinary excretion of ALA and PBG is normal. The patients also do not develop photocutaneous lesions like those with the porphyrias. Thus, the secondary porphyrinurias can usually be distinguished from the porphyrias.

Pseudoporphyria is a condition in which there are skin lesions similar to those in porphyria cutanea tarda, but serum and urine porphyrin levels are normal or only minimally elevated. This occurs in renal failure, from use of medications such as nonsteroidal antiinflammatory drugs and tetracycline, and from ultraviolet A exposure. Treatment consists of discontinuing the causative factor and protection from the sun.

### See Also the Following Articles

**Hepatitis C • Hepatocellular Carcinoma (HCC)**

### Further Reading

Anderson, K. E. (2003). The porphyrias. *In* "Hepatology" (D. Zakim and T. Boyer, eds.), 4th Ed., pp. 291–346. W. B. Saunders, Philadelphia.

Bloomer, J., and Brenner, D. (2003). The porphyrias. *In* "Schiff's Diseases of the Liver" (E. Schiff, M. Sorrell, and W. Maddrey, eds.), 9th Ed., pp. 1231–1260. Lippincott Williams & Wilkins, Philadelphia.

# Portal Hypertension and Esophageal Varices

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**ascites** Excessive accumulation of fluid in the peritoneal cavity.
**cirrhosis** Advanced liver disease characterized by distorted architecture secondary to hepatic fibrosis and regenerative nodules.
**esophageal varices** Dilated blood vessels around the esophagus.
**portal hypertension** A portal pressure >5 mmHg in the portal circulation.

**Portal hypertension is directly responsible for the development of variceal hemorrhage and ascites, the two major complications of cirrhosis. Of these complications, hemorrhage from esophageal varices is an immediately life-threatening event that is associated with a high mortality. The prevention and treatment of esophageal varices is therefore a cornerstone in the management of cirrhosis.**

## PATHOGENESIS

### Development of Portal Hypertension

The portal vein is formed by the confluence of the superior mesenteric vein and the splenic vein. It drains blood from the splanchnic bed to the liver, which is drained by hepatic veins in the inferior vena cava. Following the principles of Ohm's law, the pressure in the portal vein is determined by the portal venous inflow and the resistance to outflow from the portal vein:

$$\text{Portal Pressure} = \text{Portal venous inflow} \times \text{Resistance to outflow from the portal vein.} \quad [1]$$

Portal hypertension is initiated by an increase in resistance to portal venous outflow. Depending on the site of the increase in resistance, portal hypertension may also be classified as presinusoidal, sinusoidal, or postsinusoidal (Table I). The most common cause of portal hypertension is cirrhosis. The increased resistance found in cirrhosis is intrahepatic and primarily sinusoidal in origin. Increased sinusoidal resistance results from both a fixed component due to the architectural distortion associated with cirrhosis and a dynamic component due to altered regulation of sinusoidal vascular resistance. The latter is related to decreased nitric oxide (NO) production by the sinusoidal endothelium in cirrhosis. Cirrhosis is also associated with increased NO production in the systemic circulation, which leads to systemic arterial vasodilation and a hyperdynamic circulatory state. Mesenteric arterial dilation increases portal venous inflow and further compounds the severity of the portal hypertension.

TABLE I Causes of Portal Hypertension

| |
|---|
| **Presinusoidal** |
| **Prehepatic** |
| Splenic vein thrombosis |
| Portal vein thrombosis |
| Cavernous transformation of vein |
| Extrinsic compression of the portal vein |
| **Intrahepatic** |
| Primary biliary cirrhosis (precirrhotic stages) |
| Primary sclerosing cholangitis |
| Sarcoidosis |
| Schistosomiasis |
| **Sinusoidal** |
| Cirrhosis |
| Alcoholic hepatitis |
| Nodular regenerative hyperplasia |
| Vitamin A toxicity |
| **Posthepatic** |
| Budd-Chiari syndrome |
| Veno-occlusive disease |
| Constrictive pericarditis |
| Tricuspid valve disease |
| Severe congestive cardiomyopathy |

### Measurement of Portal Hemodynamics

Portal venous hemodynamics can be measured by hepatic venous catheterization. During this procedure, a balloon catheter is passed into the hepatic vein and the following parameters are measured:

Free hepatic venous pressure (FHVP)
= pressure in the hepatic vein measured with the balloon deflated.

Wedged hepatic venous pressure (WHVP)
= pressure in the hepatic vein measured with the balloon inflated to occlude the hepatic vein. [2]
Hepatic venous pressure gradient (HVPG)
= WHVP − FHVP.

The HVPG represents the pressure in the hepatic sinusoids and portal vein and is a measure of portal pressure.

### Development of Variceal Hemorrhage

Once portal hypertension occurs, nature decompresses the portal vein by the opening of a collateral circulation that diverts blood from the portal venous bed directly to the systemic circulation. The most common site for development of such collaterals is the gastroesophageal junction, where the collaterals form thin-walled varicose veins.

As noted above, the pressure in the varix is determined by the product of variceal blood flow and resistance. Esophageal varices do not develop at HPVG values less than 12 mm Hg. On the other hand, HVPG values greater than 12 mmHg do not directly correlate with risk of bleeding. This suggests that local factors at the level of the varices also determine an individual subject's probability of bleeding (Table II).

The risk of rupture of esophageal varices is determined by the wall tension, which is dictated by Laplace's law:

Wall tension = Transmural pressure gradient × radius / thickness of the variceal wall. [3]

Based on Laplace's law (Eq. [3] above), large varices with thin walls and a high intramural pressure are most likely to bleed. Varices in the distal esophagus have the least amount of tissue covering the esophageal veins and therefore are the most prone to bleed. Thinning of the mucosa over a varix also contributes to the risk of hemorrhage and is noted clinically by the presence of "red signs" on endoscopy (Table III). These include red wale marks, cherry red spots, hematocystic spots, and diffuse erythema. Clinical features, such as the degree of liver dysfunction and history of previous variceal bleeds, are also significant predictors of the risk of developing variceal hemorrhages.

TABLE II Risk Factors That Affect the Likelihood of Variceal Hemorrhage

| |
|---|
| Portal pressure |
| Variceal pressure |
| Variceal location |
| Variceal size |
| Variceal appearance (red signs) |
| Liver function |
| Previous variceal hemorrhage |

TABLE III Types of Endoscopic "Red Signs" on Varices

| Red signs |
|---|
| Red wale marks |
| Cherry red spots |
| Hematocystic spots |
| Diffuse erythema |

## NATURAL HISTORY

Approximately 30% of patients with compensated cirrhosis and 60% of patients with decompensated cirrhosis have esophageal varices. In those without varices, the risk of *de novo* varix development is approximately 5% annually. One-third of all patients with varices experience variceal hemorrhage. The risk of bleeding is greatest in the first year after diagnosis and can be estimated by assessment of variceal size, liver function, and presence of red signs (Table IV).

Once varices start bleeding, spontaneous hemostasis occurs in only 50% of cases. The risk factors for continued bleeding include advanced liver failure and large spurting varices. Once hemostasis occurs, there is a high risk of recurrent bleeding over the next 2–3 days, which subsides to baseline levels by 6 weeks. The risk factors for such "early rebleeding" include age >60 years, hemoglobin less than 8 g/dl on admission, renal failure, ascites, active bleeding, red signs or platelet clots on varices, and overly aggressive volume replacement. Overall, each episode of variceal hemorrhage continues to be associated with a 20–30% mortality rate.

In the long term, over 70% of survivors of an index bleed will experience recurrent hemorrhage if left untreated and a similar number will die within 1 year. The risk of late rebleeding >6 weeks is linked to severity of liver failure, ascites, presence of hepatoma, active alcoholism, and red signs.

## PRIMARY PREVENTION

### Selection of Patients for Primary Prophylaxis

The risks of variceal hemorrhage varies greatly from one patient to the next. Given the potential toxicity of

TABLE IV Estimated 1-Year Percentage Probability of Bleeding as a Function of All Possible Combinations of the Endoscopic Variables

| Red wale markings | Child's class | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | A | | | B | | | C | | |
| | *F1 | F2 | F3 | F1 | F2 | F3 | F1 | F2 | F3 |
| − | 6 | 10 | 15 | 10 | 16 | 26 | 20 | 30 | 42 |
| + | 8 | 12 | 19 | 15 | 23 | 33 | 28 | 38 | 54 |
| ++ | 12 | 16 | 24 | 20 | 30 | 42 | 36 | 48 | 64 |
| +++ | 16 | 23 | 34 | 28 | 40 | 52 | 44 | 60 | 76 |

Based on data from Defranchis, R. (1998). Prediction of the first variceal hemorrhage in patients with cirrhosis of the liver and esophageal varices. *N. Engl. J. Med.* 319, 983.

*F1, F2, and F3 are progressively larger varices.

the available treatment approaches, it is imperative to identify those at greatest risk of bleeding and thus most likely to benefit from primary prophylaxis. This is achieved by clinical assessment and by endoscopy of all patients with cirrhosis (Table IV). Those with medium to large varices are generally considered for primary prophylaxis. If no varices are seen, follow-up endoscopy is generally recommended at 2-year intervals although the cost-effectiveness of this approach remains to be established.

### *Beta-Blockers*

Nonselective beta-blockers are the first-line treatment for primary prophylaxis of variceal bleeding in cirrhosis. They decrease portal pressure by causing beta-blockade, which allows unopposed α-adrenergic-mediated mesenteric arteriolar vasoconstriction. This decreases portal venous inflow and thus portal pressure. At high doses, bradycardia and decreased cardiac output also contribute to this effect.

The efficacy and safety of propranolol and nadolol have been evaluated in a large number of clinical trials. Meta-analyses have shown that beta-blockers reduce the index bleed by approximately 45% and also decrease mortality due to bleeding by 50%. However, this is not accompanied by an overall improvement in survival. The best predictor of successful primary prophylaxis is the ability to produce a sustained drop in HVPG by 20% or to values less than 12 mm Hg. It has therefore been recommended that hepatic venous catheterization be performed prior to and 3 months after initiation of treatment with beta-blockers. The cost-effectiveness of such an approach remains to be validated and the facilities to perform HVPG measurements are not universally available. In their absence, the dose of beta-blockers is titrated to achieve a reduction in heart rate (HR) to 25% of baseline, or to 55–60 beats per minute, and is limited by the development of side effects. Regrettably there is a poor correlation between HR and reduction in portal pressure.

Approximately 20% of patients do not respond to beta-blockers and an additional 20% are unable to tolerate beta-blockers. Risk factors associated with high failure rates include a smaller decrement in resting heart rate, younger age, advanced liver failure, large variceal size, and lower doses of beta-blockers. Over time, many patients also develop tachyphylaxis due to increased veno-collateral resistance within the liver. The side effects of beta-blockers include precipitation or worsening of congestive heart failure, sinus bradycardia, increased airway resistance, exacerbation of peripheral vascular disease, facilitation of hypoglycemia, depression, fatigue, and sexual dysfunction.

### *Nitrates*

Nitrates act as venodilators, in turn decreasing venous return and therefore decreasing cardiac output. Systemic venodilation also decreases postsinusoidal resistance and consequently decreases portal hypertension. Initial clinical trials comparing isosorbide mononitrate (ISMN) alone versus propranolol alone found ISMN to be as effective as propranolol for the prevention of bleeding; however, those over 50 years of age had a poorer survival with ISMN. Another recent study also showed that ISMN did not reduce the incidence of variceal bleeding or survival in patients with varices unable to tolerate beta-blockers. Thus, nitrates are not recommended as monotherapy for primary prophylaxis of variceal hemorrhage.

## Nitrates Plus Beta-Blockers

A combination of ISMN with a nonselective beta-blocker has a synergistic effect on portal pressures. Clinical trials have shown combination therapy to be superior to beta-blockers alone. Such benefits are most pronounced in those with relatively preserved liver function. The use of combination therapy is usually restricted to such individuals or those who do not have a sustained improvement in HVPG after starting beta-blockers.

### *Endoscopic Therapy*

Endoscopic sclerotherapy (EST) is performed by injection of a sclerosant into varices that produce variceal thrombosis and obliteration. Endoscopic variceal ligation (EVL) is performed by placing an elastic O ring around the neck of a varix and subsequently causing strangulation of the vein. Thrombosis and

esophagitis/esophagitis of the necrotic mucosa follow, leading to the obliteration of the varix. The use of EST for primary prophylaxis has been discontinued since a large multicenter trial showed increased mortality in those undergoing EST. On the other hand, compared to no treatment, EVL decreases the risk of index bleeding by 64% and decreases overall mortality by 45%. Compared to beta-blockers, EVL reduces the risk of bleeding by approximately 52% but this does not translate into a survival advantage. EVL is currently recommended for those with large varices who are unable to tolerate beta-blockers. There are currently no published data comparing a combination of beta-blockers with band ligation to either beta blockers or EVL alone.

*Summary*

All patients with cirrhosis should undergo endoscopy to assess the risk of variceal hemorrhage. Those at intermediate or high risk should undergo treatment with a nonselective beta-blocker, e.g., propranolol or nadolol. The dose should be titrated to achieve a resting heart rate of 55–60 beats/min. Ideally, the HVPG should be measured before and 1–3 months after starting therapy to identify poor responders to therapy. Such individuals may be treated by addition of nitrates or by EVL. EVL should also be considered in those who cannot tolerate pharmacologic treatment (Fig 1).

## MANAGEMENT OF ACTIVE VARICEAL BLEEDING

There are three goals of management of active variceal hemorrhage: (1) hemodynamic resuscitation; (2) prevention of complications; and (3) achievement of hemostasis. Therapy must be directed at all three goals simultaneously in order to optimize outcomes. Hemodynamic resuscitation must be aggressively pursued and the hemoglobin maintained between 9 and 10 g/dl (Table V). The urine output should be carefully monitored and fluid infusions titrated to maintain a urine output greater than 30 cc/h. The airway must be protected and the patient intubated if he or she is unable to clear secretions in the airway. Blood and ascites fluid should be obtained for culture, and prophylactic broad-spectrum antibiotics, e.g., cefotaxime, should be administered intravenously until culture results are determined. In the absence of positive cultures or spontaneous bacterial peritonitis (SBP), treatment may be switched to an oral quinolone, e.g., norfloxacin, for up to 2 weeks for primary prophylaxis of SBP.

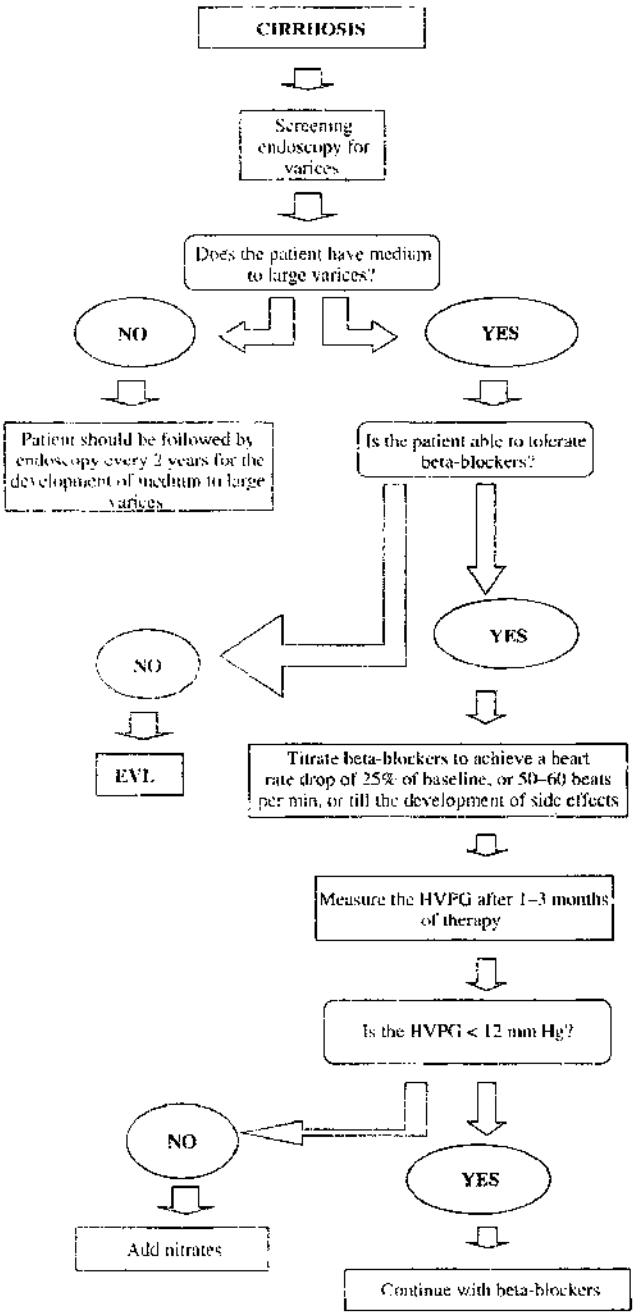


**FIGURE 1** Primary prevention. These are only general guidelines and appropriate therapy should be based on the patient's individual circumstances and the expertise available.

### First-Line Therapy for Achievement of Hemostasis

#### *Pharmacologic Treatment*

**Vasopressin and its analogues** Vasopressin interacts with arterial smooth muscle receptors to induce splanchnic arteriolar vasoconstriction, decreasing blood flow to all splanchnic organs and resulting in a decline in portal pressure. The use of vasopressin has

**TABLE V Management of Patients with Active Variceal Hemorrhage**

| |
|---|
| Hemodynamic resuscitation |
| Maintain hemoglobin between 9 and 10 g/dl |
| Replace platelets in actively bleeding patients when levels fall below 50,000/ml |
| Airway protection |
| Intubate for aspiration pneumonia prevention |
| Renal support |
| Preserve urine output above 50 ml/h |
| Avoid nephrotoxins |
| Sepsis prevention |
| Obtain blood and ascites fluid for culture and prophylactic broad-spectrum antibiotics |
| Neurologic support |
| Monitor mental status and avoid sedation |
| Metabolic support |
| Monitor and treat electrolyte abnormalities |
| Monitor and treat endocrine abnormalities |
| Treat alcohol withdrawal when indicated |

declined due to its side effects, which include myocardial and intestinal ischemia, hypertension, bradycardia, hyponatremia, and fluid retention. Some of these effects can be minimized while enhancing therapeutic efficacy by concomitant administration of nitroglycerin.

Terilipressin is an inert analogue of vasopressin; due to its slow activation, terlipressin has less toxicity than vasopressin alone or in combination with nitroglycerin. Terlipressin has also been shown to be better than placebo or vasopressin and similar to somatostatin or balloon tamponade in acute variceal bleeding management. Currently, Terlipressin is not available for clinical use in the United States.

**Somatostatin and its analogues** Somatostatin inhibits the release of splanchnic vasodilators hormones, such as glucagon and vasoactive intestinal peptide, thereby increasing mesenteric arteriolar tone and decreasing portal venous inflow. Somatostatin is as effective as vasopressin in the control of the bleeding and has a lower risk of adverse effects. The beneficial effects of somatostain over vasopressin have made somatostatin the pharmacological treatment of choice for active bleeding even though no decrease in mortality has been clearly proven. Circulating somatostatin has a half-life of only a few minutes and this has led to use of its longer acting analogue, octreotide. Although there is some controversy over the relative efficacy of octreotide versus somatostatin, the use of octreotide with EVL or EST has been found to be superior to either EVL or EST alone in terms of achieving hemostasis or prevention of early rebleeding. However, no change in overall mortality has been demonstrated with either somatostatin or octreotide.

**Endoscopic therapy** EST is highly effective in achieving hemostasis (70–90%) and decreasing the risk of early rebleeding (20–30%) compared to vasopressin or balloon tamponade. EST is as effective as somatostatin or octreotide but less effective than combination therapy. Unfortunately, endoscopic sclerotherapy has a 10 to 30% complication rate (Table VI) and a 0.5 to 2% mortality rate. EST and EVL are comparable in terms of efficacy when used for active variceal hemorrhage. EVL has a lower rebleeding rate, lower mortality rate, and lower incidence of complication than EST; however, in cases of severe bleeding, limitation of the field of vision makes EVL more challenging.

## FAILURE OF FIRST-LINE THERAPY (SECOND-LINE TREATMENT)

Approximately 10–20% of patients either continue to bleed despite first-line therapy or experience early rebleeding. Such patients are at great risk of dying from exsanguination and from the complications of variceal hemorrhage, such as aspiration, sepsis, and hepatorenal syndrome. It is therefore imperative to quickly stabilize the patient and perform a salvage procedure in such cases.

### Balloon Tamponade

This technique utilizes a balloon catheter that mechanically tamponades the bleeding varix. There are several types of balloon catheters that are used for this purpose and all can quickly achieve hemostasis. Unfortunately, there is a very high risk of bleeding when the

**TABLE VI Complications of Sclerotherapy**

| |
|---|
| Local |
| Stricture formation |
| Ulceration |
| Perforation |
| Bleeding |
| Esophageal dysmotility |
| Pain/odynophagia |
| Regional |
| Pleural effusion |
| Mediastinitis |
| Acute gastric dilation |
| Systemic |
| Pulmonary edema |
| Aspiration pneumonia |
| Sepsis |
| Spontaneous bacterial peritonitis |
| Adult respiratory distress syndrome |
| Portal vein thrombosis |

balloon is deflated. Moreover, prolonged insufflation of the balloon can lead to mucosal necrosis and ulceration. Finally, balloon tamponades occlude the gastroesophageal junction and prevent clearance of swallowed saliva and secretions, thereby creating a high-risk situation for pulmonary aspiration. These risks can be minimized by protecting the airway by intubation and by the use of an esophageal aspiration port. Balloon tamponade is used only as a temporary measure while preparations are made for a definitive procedure.

## Surgery

The surgical options available for acute variceal bleeding consist of shunt or nonshunt operations. Shunt operations decompress the portal system and are total, partial, or selective. Total shunts redirect all portal blood away from the liver and are highly effective in terminating active bleeding and preventing future bleeds. Unfortunately, approximately 40 to 50% patients who undergo total shunts will have chronic or recurrent encephalopathy and accelerated progression of underlying liver failure. Such operations are not performed as first-line therapy because the outcomes with EST have been shown to be comparable to those for urgent portacaval shunt surgery.

Partial shunts preserve some hepatic portal perfusion and in turn reduce the rates of encephalopathy and liver failure. Nonetheless, the incidence of early shunt thrombosis is relatively high. Selective shunts divide the portal system into a decompressed variceal compartment and a hypertensive superior mesenteric–portal vein compartment. The most prominent selective shunt is distal splenorenal shunt (DSRS), which maintains a certain degree of liver perfusion, avoids dissection of the hilus, and therefore does not interfere with subsequent liver transplantation. The drawback to DSRS is that sinusoidal hypertension persists, and ascites, which does not resolve, can be difficult to manage. Nonshunt operations include esophageal transection and devascularization. Esophageal transection is highly effective in arresting bleeding from esophageal varices unresponsive to medical therapy, but rebleeding from gastric varices and the transection line is a problem in 50% of patients. The complete devascularization (Suguira) procedure is highly effective in controlling active hemorrhage. Such operations carry a rebleeding rate of 2 to 37% and have a reported mortality rate of 5% or higher.

## Transjugular Intrahepatic Portosystemic Shunts

Transjugular intrahepatic portosystemic shunts (TIPS) is an angiographic procedure in which a fenestrated metal stent is deployed between the intrahepatic portion of the portal vein and the hepatic vein, thereby creating a "side to side" porta-systemic anastamosis. The ability to decompress the portal vein without the need for general anesthesia or major surgery has led to a resurgence in interest in portal decompression in patients with active and refractory variceal hemorrhage. TIPS can be performed successfully in over 90% of cases and achieves hemostasis in over 90% of cases. It also has been shown to improve survival in this group of very sick individuals. Thus, TIPS is the procedure of choice for salvage therapy in high-risk individuals who continue to bleed or have severe early rebleeding after first-line therapy.

TIPS is associated with numerous complications (Table VII) including encephalopathy, hemolysis, and thrombosis. In the long term, virtually all patients develop recurrent portal hypertension due to the ingrowth of tissue from the surrounding liver, which forms a pseudo-intimal lining in the shunt. This requires patients to undergo periodic sonographic screening for shunt patency after TIPS placement. Unfortunately, sonography is specific but relatively insensitive for the diagnosis of shunt stenosis.

## Summary

Management of active variceal bleeding includes hemodynamic resuscitation, prevention and treatment of complications, and halting the bleed. Somatostatin, octreotide, or terlipressin may be started in the emergency room and given in conjunction with EST or EVL. Those who fail first-line therapy should be stabilized and a definitive procedure (TIPS for high-risk cases and TIPS or surgery for average-risk cases) performed quickly (Fig. 2).

TABLE VII Complications of Transjugular Intrahepatic Portosystemic Shunts (TIPS)

| |
|---|
| Procedure-linked complications |
| Neck hematoma |
| Perihepatic hematoma |
| Cardiac arrhythmias |
| Rupture of liver capsule |
| Puncture of portal vein |
| Complications related to portosystemic shunting |
| Hepatic encephalopathy |
| Increased susceptibility to bacteremia |
| Liver failure |
| Stent-related complications |
| TIPS-associated hemolysis |
| Infection of the stents |
| Stent stenosis or malfunction |

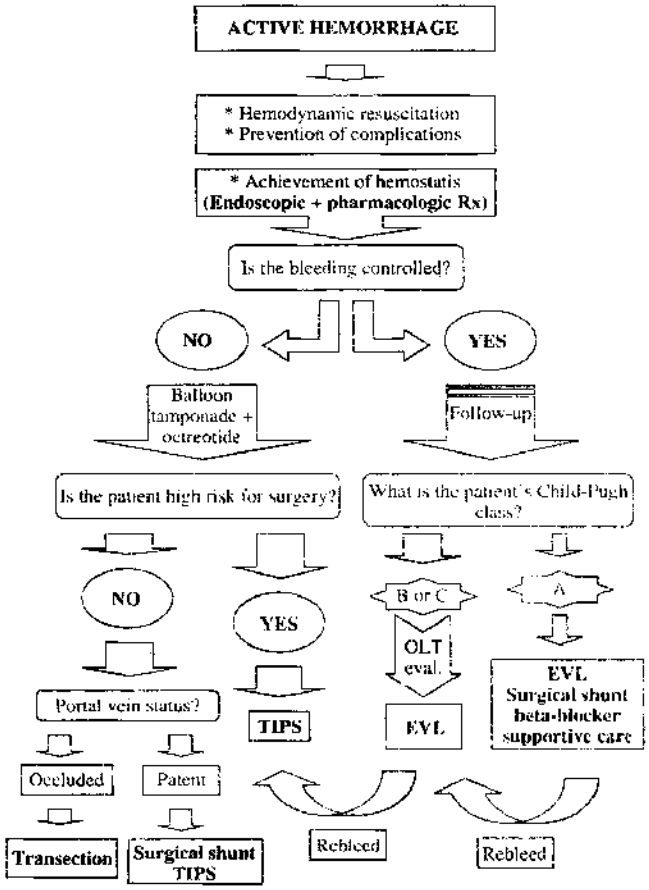


**FIGURE 2** Management of active hemorrhage. These are only general guidelines and appropriate therapy should be based on the patient's individual circumstances and the expertise available.

## SECONDARY PREVENTION

Given the high recurrence rate of rebleeding, attention must be given to providing secondary prophylaxis to those who survive an index bleed. The treatment modalities available are identical to those used for primary prophylaxis and acute management.

### Endoscopic Therapy

EVL is currently the procedure of choice for the secondary prevention of esophageal variceal hemorrhage. Compared to sclerotherapy, EVL showed earlier variceal obliteration, fewer complications, less rebleeding, and a trend toward decreased mortality. The combination of EST and EVL does not provide any advantage over EVL alone and is actually associated with higher mortality.

### Beta-Blockers

Studies on the effect of beta-blockers as secondary prevention suggest that beta-blockers reduce the risk of bleeding by approximately 40% and risk of death by 20%. A crucial predictive factor in the effectiveness of beta-blockers is its ability to decrease HPVG by 20% or more. Good responders to beta-blockers are considered patients with 20% or more reduction in HPVG and are much less likely (2 of 25 versus 23 of 44) to have episodes of rebleeding within the first 28 months of therapy. Patients with well-preserved hepatic synthetic function seem to benefit the most from beta-blocker therapy. Overall, EST is associated with a lower rebleed rate than beta-blockers but the effects of these therapies on mortality are similar. Recent studies indicate that EVL is at least as effective as beta-blockers for the prevention of recurrent variceal bleeding.

### Beta-Blocker Plus Oral Nitrates

Combination pharmacologic therapy has been shown to be more effective than EST or EVL in two studies of patients with well-preserved liver function from the same center. In two other studies, combination therapy was found to be equally as effective as EVL. The potential role of combination therapy is evolving and it may become an alternative to EVL for the prevention of recurrent variceal hemorrhage.

### Transjugular Intrahepatic Portosystemic Shunts

TIPS decreases the risk of recurrent bleeding more effectively than endoscopic therapy. However, this is not associated with a survival advantage. There is also an increased risk of encephalopathy following TIPS. In some cases, TIPS is followed by progressive liver failure. Finally, patients require multiple follow-up sonograms and angiograms for the detection and treatment of shunt stenosis. These considerations have relegated the role of TIPS to a salvage treatment in those who rebleed despite adequate endoscopic and pharmacologic therapy.

### Surgery

The efficiency of surgical treatment for rebleeding prevention is offset by studies showing that the survival outcome after sclerotherapy is identical to or better than that achieved by surgery. In addition, postoperative mortality and complications are more considerable with surgery. Regardless of the limitations of surgery, surgery remains a valuable form of treatment in selected patients who are refractory to endoscopic therapy. The outcomes after surgery are best in those with well-preserved liver functions.

### Liver Transplant

Orthotopic liver transplant (OLT) is the only remedy that provides long-term treatment for prevention of

rebleeding, hepatic decompensation, and death. OLT provides an 80–90% 1-year survival rate and a 60% 5-year survival rate. OLT may be considered in those with recurrent variceal bleeds or those with severe liver failure. Unfortunately, this option is not available to many subjects and, when available, is limited by organ availability.

## See Also the Following Articles

**Ascites • Budd–Chiari Syndrome • Cholangitis, Sclerosing • Cholestatic Diseases, Chronic • Cirrhosis • Hepatic Circulation • Portal Vein Thrombosis • Sinusoidal Obstruction Syndrome (Hepatic Venoocclusive Disease) • Somatostatin • Upper Gastrointestinal Bleeding • Variceal Bleeding**

## Further Reading


Banares, R., Albillos, A., Rincon, D., *et al.* (2002). Endoscopic treatment versus endoscopic plus pharmacologic treatment for acute variceal bleeding: A meta-analysis. *Hepatology* **35**, 609–615.

Beppu, K., Inokuchi, K., Koyanagi, N., *et al.* (1981). Prediction of variceal hemorrhage by esophageal endoscopy. *Gastrointest. Endosc.* **27**, 213–218.

Bomzon, A., and Blendis, L. M. (1994). The nitric oxide hypothesis and the hyperdynamic circulation in cirrhosis. *Hepatology* **20**, 1343–1350.

Cales, P., Desmorat, H., Vinel, J. P., *et al.* (1990). Incidence of large oesophageal varices in patients with cirrhosis: Application to prophylaxis of first bleeding. *Gut* **31**, 1298–1302.

Cello, J. P., Grendell, J. H., Crass, R. A., Weber, T. E., and Trunkey, D. D. (1987). Endoscopic sclerotherapy versus portacaval shunt in patient with severe cirrhosis and acute variceal hemorrhage: Long-term follow-up. *N. Engl. J. Med.* **316**, 11–15.

D'amico, G., and Luca, A. (1997). Natural history. Clinical–haemodynamic correlations: Prediction of the risk of bleeding. *Bailliere Clin. Gastroenterol.* **11**, 243–256.

D'amico, G., Morabito, A., and Pagliaro, L. (1986). Six week prognostic indicators in upper gastrointestinal hemorrhage in cirrhotics. *Front. Gastrointestinal. Res.* **9**, 247.

D'amico, G., Pagliaro, L., and Bosch, J. (1995). The treatment of portal hypertension: A meta-analytic review. *Hepatology* **22**, 332–354.

Garcia-Tsao, G., Groszmann, R. J., Fisher, R. L., Conn, H. O., Atterbury, C. E., and Glickman M. (1985). Portal pressure, presence of gastroesophageal varices and variceal bleeding. *Hepatology* **5**, 419–424.

Graham, D. Y., and Smith, J. L. (1981). The course of patients after variceal hemorrhage. *Gastroenterology* **80**, 800–809.

Imperiale, T. F., and Chalasani, N. (2001). A meta-analysis of endoscopic variceal ligation for primary prophylaxis of esophageal variceal bleeding. *Hepatology* **33**, 802–807.

Imperiale, T. F., Teran, J. C., and McCullough, A. J. (1995). A meta-analysis of somatostatin versus vasopressin in the management of acute esophageal variceal hemorrhage. *Gastroenterology* **109**, 1289–1294.

Laine, L., and Cook, D. (1995). Endoscopic ligation compared with sclerotherapy for treatment of esophageal variceal bleeding: A meta-analysis 3. *Ann. Intern. Med.* **123**, 280–287.

Poynard, T., Cales, P., Pasta, L., *et al.* (1991). Beta-adrenergic-antagonist drugs in the prevention of gastrointestinal bleeding in patients with cirrhosis and esophageal varices: An analysis of data and prognostic factors in 589 patients from four randomized clinical trials. Franco-Italian Multicenter Study Group. *N. Engl. J. Med.* **324**, 1532–1538.

Sanyal, A. J., Freedman, A. M., Luketic, V. A., *et al.* (1997). The natural history of portal hypertension after transjugular intrahepatic portosystemic shunts. *Gastroenterology* **112**, 889–898.

Sanyal, A. J., Freedman, A. M., Luketic, V. A., *et al.* (1996). Transjugular intrahepatic portosystemic shunts for patients with active variceal hemorrhage unresponsive to sclerotherapy. *Gastroenterology* **111**, 138–146.

# Portal Vein Thrombosis

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**ascites** Presence of fluid in the peritoneal cavity.
**hepatic encephalopathy** Neuropsychiatric manifestations associated with liver disease.
**hypersplenism** Reduction in two or more of the formed elements of blood as a manifestation of splenomegaly; associated with a normal bone marrow.
**portal hypertension** Elevation in pressure in the portal venous system. Bleeding from esophageal varices, ascites, and hepatic encephalopathy are complications of portal hypertension.
**portal venous system** Vessel pathway beginning and ending in the capillaries.

**Portal vein thrombosis is a common cause of portal hypertension in the absence of chronic liver disease, especially in children. The clinical manifestations of portal vein thrombosis depend both on the extent and the duration of the thrombosis. Thus, patients may present with abdominal pain, diarrhea, or gastrointestinal bleeding.**

## NORMAL PORTAL CIRCULATION

The portal vein serves to drain almost the entire gastrointestinal tract, spleen, pancreas, and gallbladder. The portal vein is approximately 7 cm in length and courses in the hepatoduodenal ligament, usually dorsal to the bile duct and hepatic artery, and divides into two lobar veins, the left and the right, before entering the portal fissure. The superior pancreaticoduodenal and left gastric veins drain into the portal vein near its origin. The upper 5 cm of the portal vein usually receives no venous branches. The umbilical vein and the paraumbilical veins may drain into the left branch of the portal vein, whereas the cystic vein drains into the right portal vein.

The portal vein constitutes the major oxygen supply to the liver. Portal venous flow is approximately 1150 ml/min, as opposed to hepatic arterial flow, which is only 350 ml/min, resulting in total liver blood flow of 1500 ml/min. The portal vein supplies between 50 and 70% of the oxygen to the liver, especially during the fasting state.

## PATHOGENESIS OF PORTAL VEIN THROMBOSIS

Portal vein thrombosis in children is usually a result of umbilical cord sepsis or follows catheterization of the umbilical vein. In adults, portal vein thrombosis is secondary to diseases that result in increased coagulability of the blood. These include heritable or acquired disorders of coagulation, cancer (especially hepatocellular cancer), intraabdominal sepsis, inflammatory bowel disease, and postoperative states. Portal vein thrombosis may result from extension of thrombosis in the vein following splenectomy. In young women, oral contraceptive use is an additional risk factor. In patients with cirrhosis of the liver, portal vein thrombosis occurs in less than 1% of patients. However, among patients with cirrhosis and with portal vein thrombosis, hepatocellular carcinoma occurs in up to 25% of patients.

## CLINICAL PRESENTATION

Portal vein thrombosis is classified as acute, subacute, or chronic. Acute portal vein thrombosis manifests as abdominal pain that may be associated with diarrhea. The pain is nonspecific. Radiological imaging in these patients demonstrates thrombosis of the portal vein without significant collateral circulation. Symptoms are usually present for days. In subacute portal vein thrombosis, symptoms are present for days to weeks, and imaging studies show a collateral circulation in addition to the portal vein thrombosis. In chronic portal vein thrombosis, the portal vein may not be visualized and is replaced by an extensive network of collateral veins, the so-called cavernous transformation of the portal vein. When portal vein thrombosis occurs in patients with cirrhosis of the liver, additional clinical features include further deterioration in liver function manifesting as ascites, and worsening encephalopathy.

Physical examination of patients with portal vein thrombosis is nonspecific. Patients in whom thrombosis has extended into the smaller veins of the portal

 

circulation, especially those closely applied to the bowel, may have abdominal tenderness. When the small vessels are thrombosed, there is an increased risk of developing ischemia of the bowel that may progress to infarction and peritonitis. Such patients are more likely to have hemodynamic instability.

## DIAGNOSIS

Routine blood tests are not helpful in making a diagnosis of portal vein thrombosis. Diagnosis is usually made with radiological investigations, such as Doppler ultrasonography or, preferably, computer tomography (CT) scans of the abdomen. Magnetic resonance imaging is helpful but not often used in the initial investigation of these patients. Mesenteric angiogram is the gold standard in demonstrating thrombosis in the portal vein, but is usually required only if the plan involves surgery to decompress the portal system. Investigations are also carried out to exclude inherited and acquired disorders of coagulation.

## TREATMENT

Treatment of portal vein thrombosis is challenging. Long-term anticoagulation is recommended in all patients with portal vein thrombosis with an underlying thrombophilia. Anticoagulation is also recommended in patients with an acute or subacute presentation, provided these are no contraindications such as active bleeding. In the rare patient who presents within 24–48 hours of the onset of portal vein thrombosis, thrombolytic therapy in an attempt to dissolve the clot may be tried. Patients with chronic portal vein thrombosis present predominantly as portal hypertension manifesting with variceal bleeding and hypersplenism. In such patients with large esophageal varices, anticoagulation is not recommended. Patients who present with gastrointestinal bleeding can be treated either by injection of a sclerosant into the varices or by band ligation of the varices. Surgical shunts are used in patients in whom bleeding cannot be controlled by conservative measures; this involves connecting a branch of the portal venous system, either the splenic vein or the superior mesenteric vein, to a systemic vein, such as the renal vein or inferior vena cava.

### See Also the Following Articles

**Ascites • Hepatic Encephalopathy • Portal Hypertension and Esophageal Varices**

### Further Reading

Condat, B., Pessionem, F., Hillarre, S., Denninger, M. H., Guillin, M. C., Polliquin, M., Hadengue, A., Erlinger, S., and Valla, D. (2001). Current outcome of portal vein thrombosis in adults: Risk and benefit of anticoagulant therapy. *Gastroenterology* **120**, 490–497.

Kumar, S., Sarr, M. G., and Kamath, P. S. (2001). Mesenteric venous thrombosis. *N. Engl. J. Med.* **345**, 1683–1688.

Okuda, K., Ohnishi, K., Kimura, K., Matsutani, S., Sumida, M., Goto, N., Musha, H., Takashi, M., Suzuki, N., and Shinagava, T. (1985). Incidence of portal vein thrombosis in liver cirrhosis: An angiographic study in 708 patients. *Gastroenterology* **89**, 279–286.

# Postprandial Motility

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**gastrocolic reflex** Changes in the motility of the large intestine following ingestion of a meal.
**migrating motor complex** Motility pattern of the interdigestive state in the small intestine.
**power propulsion** Motility pattern that propels the intraluminal contents rapidly over long distances in the small and large intestine.

**Ingestion of a nutrient meal initiates specialized patterns of postprandial motility in the stomach and small and large intestine. Postprandial motility in the reservoir of the upper stomach relaxes the gastric wall to accommodate the increasing volume during active ingestion of a meal. Postprandial motility in the antral region of the stomach triturates the contents to particles of sufficiently small size for effective emptying into the small intestine. Mixing movements are the characteristic motility pattern in the small intestine, and the increased incidence of mass movements and a generalized increase in mixing-like movements occur in the large intestine following ingestion of a meal.**

## INTRODUCTION

Following ingestion of a meal, when the gastric wall is not relaxing in response to the swallowing and filling process that initiates postprandial motility in the upper stomach, the muscles in the wall of the gastric reservoir contract, exerting controlled compressive forces on the contents of the upper stomach. In the antral stomach region, the postprandial motility process effects pulverization of food particles. Particulates in the stomach are not emptied until they are reduced to sizes less than about 5 mm. The reduced size of the particles increases the surface area for action by digestive enzymes in the small intestine. In the small intestine, mixing movements, the characteristic motility pattern of the fed state, are initiated. (The terms "digestive state" and "fed state" are used alternatively to describe the state of the gut after a meal.) The mixing movements start with the first ingestion of a nutrient meal and are coincident with termination of the motility pattern that characterizes the interdigestive state (i.e., the migrating motor complex). Mixing movements function to blend pancreatic, biliary, and intestinal secretions with nutrients in the small intestine and bring products of digestion into contact with the absorptive surfaces of the mucosa.

Power propulsion, a programmed motor event in the transverse and descending colon, is also associated with intake of a meal. This form of motor behavior fits the general pattern of neurally coordinated peristaltic propulsion and results in the mass movement of feces over extended distances toward the anus. Mass movements may be triggered by increased delivery of ileal contents into the ascending colon following a meal. Gastrocolic reflex is a term used to refer to the increased incidence of mass movements and a generalized increase in mixing-like movements that occur in the large intestine following ingestion of a meal.

## MIXING MOVEMENTS

Mixing movements of the small intestine are also called segmenting movements or segmentation due to their appearance on X-ray films of the small intestine. The mixing pattern of motility is programmed by the enteric nervous system. In the mixing pattern, the behavior of the musculature is organized to propel luminal contents in both directions over short distances. This is in contrast to other forms of propulsive motility that move the luminal contents in one direction over extended lengths of intestine. Mixing movements consist of circumferential muscle contraction in segments separated on either end by relaxed receiving segments. The receiving segments appear as sacculations with increased cross-sectional diameter on X-ray images of the small intestine (Fig. 1). Mixing occurs as the contents are forcefully propelled into the receiving segments from both directions. Each segmental contraction and relaxed receiving segment reflects the occurrence of stereotypic peristalsis that does not propagate beyond a single segment. Mixing movements are, in effect, the occurrence of ultrashort peristalsis that is repeated at multiple sites along the intestine. As is the case for propulsion over greater distances in other patterns of motility, the basic peristaltic neural reflex (i.e., contraction above

 

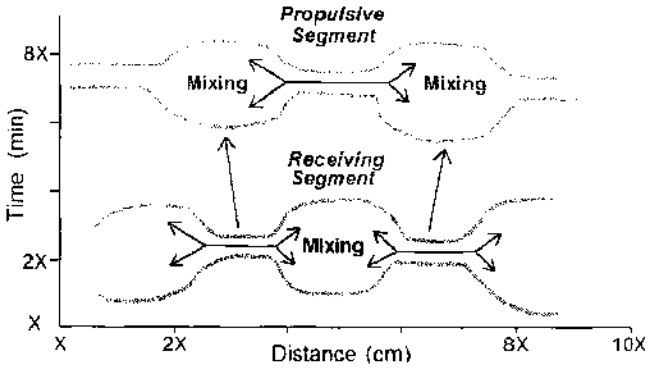


FIGURE 1 The postprandial pattern of small intestinal motility is characterized by mixing movements. Mixing movements consist of propulsive and receiving segments as described for the stereotypic pattern of behavior of the circumferential and longitudinal muscle layers during peristalsis. They can be viewed as short-distance peristaltic propulsion. The postprandial pattern of motility consists of propulsive segments separated by receiving segments, occurring with apparent randomness at many sites along the intestine. Mixing of the luminal contents occurs in the receiving segments. Over time, cyclic conversion of receiving segments to propulsive segments occurs coincident with the conversion of propulsive segments to receiving segments.

and relaxation of the intestinal wall below) underlies the mixing motility pattern. Postprandial segmentation is a mechanism for the mixing and stirring of luminal contents in the receiving segments. The enteric neural program for mixing is cyclic, with receiving segments converting to contracting segments and contracting segments becoming receiving segments. Segmenting movements occur with the same intervals as electrical slow waves or at multiples of the shortest slow-wave interval in the particular region of intestine.

Command signals transmitted from the brain to the small intestine by the vagus nerves are important for the conversion from the interdigestive motility pattern to the digestive pattern. After interruption of transmission in the vagus nerves, a larger quantity of ingested food is necessary for termination of the interdigestive motor pattern, and interruption of the migrating motor complex is often incomplete.

Evidence of vagal commands for the digestive motor pattern has been obtained in animals with cooling cuffs placed surgically around each vagus nerve. During the fed pattern, cooling and blockade of impulse transmission in the nerves results in interruption of the fed pattern of mixing movements. When the vagus nerves are blocked during the fed pattern, migrating motor complexes reappear in the intestine, but not in the stomach. With warming of the nerves and release of neural blockade, the fed pattern returns.

## See Also the Following Articles

**Barostat • Basic Electrical Rhythm • Colonic Motility • Duodenal Motility • Gastric Emptying • Gastric Motility • Gastro-colic Reflex • Ileal Brake • Migrating Motor Complex • Power Propulsion • Pylorus • Small Intestinal Motility**

## Further Reading

Hall, K., el-Sharkawy, T., and Diamant, N. (1986). Vagal control of canine postprandial upper gastrointestinal motility. *Am. J. Physiol.* 250, G501–G510.

Wood, J. (1994). Physiology of the enteric nervous system. *In* "Physiology of the Gastrointestinal Tract" (L. Johnson, D. Alpers, J. Christensen, E. Jacobson, and J. Walsh, eds.), 3rd Ed., Vol. 1, pp. 423–482. Raven Press, New York.

Wood, J. (2003). Neurogastroenterology and digestive motility. *In* "Medical Physiology" (R. Rhoades and G. Tanner, eds.), 2nd Ed., Chap. 26, pp. 449–480. Lippincott Williams & Wilkins, Baltimore.

# Pouchitis

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**diversion colitis** A characterisitic mucosal inflammation that typically occurs whenever the colon is excluded from the intestinal stream and that subsides when intestinal continuity is restored.

**kock pouch (continent ileostomy)** A reservoir constructed, following colectomy, from approximately 40 cm of ileum much like a pelvic pouch (q.v.), but with the modification of a one-way nipple valve accessed by intubation directly through the anterior abdominal wall.

**probiotics** Live microorganisms that confer health benefits through any one of a number of mechanisms, such as therapeutic modification of the enteric flora.

**Pouchitis denotes mucosal inflammation occurring in an ileal reservoir following total colectomy, usually for ulcerative colitis or familial adenomatous polyposis. The incidence of this disorder is much higher in patients with underlying chronic idiopathic inflammatory bowel disease than in those with genetic neoplastic syndromes, but it occurs in both Kock pouches (continent ileostomies) and pelvic pouches. The condition is manifested clinically by increased stool frequency, urgency, diarrhea, bleeding, and abdominal pain and often by fever or other constitutional complications.**

## DIAGNOSIS

Since other conditions may produce the same clinical syndrome as pouchitis, definitive diagnosis requires endoscopic and histologic confirmation. Characteristic endoscopic features include diffuse mucosal erythema, edema, friability, hemorrhage, and ulceration. The histologic picture is typically one of acute and/or chronic inflammatory infiltrate, villous atrophy, and crypt hyperplasia.

## DIFFERENTIAL DIAGNOSIS

Conditions that mimic pouchitis generally carry very different prognostic and therapeutic implications. It is therefore essential to distinguish pouchitis from other complications such as mechanical outflow obstruction, local sepsis, Crohn's disease, or intestinal dysmotility. A defunctionalized pouch may also manifest the mucosal changes associated with "diversion colitis," but these should regress once intestinal continuity is reestablished.

## NATURAL HISTORY

Nearly half of all ulcerative colitis patients with ileal pouches will experience at least one acute episode of pouchitis. For almost any purpose of discussion, however, it is useful to consider pouchitis as occurring in several distinct phenotypic categories:

- single acute episode;
- one or two acute episodes per year;
- more than two acute episodes per year, each responding to medical therapy;
- frequent episodes requiring chronic maintenance therapy to prevent recurrence;
- chronic refractory pouchitis, not responding to medical therapy.

Although approximately 50% of ulcerative colitis patients with ileal pouches will not suffer even one bout of pouchitis during a 5- to 10-year follow-up, the remaining 50% will be distributed approximately as follows: single episode or only one or two episodes per year, 10%; more than two responsive episodes per year, 25%; chronic pouchitis requiring maintenance therapy, 10%; and chronic refractory pouchitis, 5%. These specific frequencies may of course vary from series to series, but it is generally agreed that most pouchitis cases are responsive to acute medical therapy (see below), with only approximately 10–15% of cases (i.e., approximately 5–7% of all ulcerative colitis patients with pouches) proving to be chronic and unremitting.

## PATHOPHYSIOLOGY

The current understanding of the mechanisms underlying pouchitis is limited to theory and conjecture. Nonetheless, most current concepts are based on two undisputed observations. The first is that the overwhelming majority of cases, over 90%, are at least

 

initially responsive to antibiotics. Hence, there must be a microbiologic component to the disease. The second universal finding is that although pouchitis is experienced by nearly half of ulcerative colitis patients with ileal pouches, this complication is extremely rare (albeit not totally unreported) in familial adenomatous polyposis. Therefore, there must also be an element of underlying host susceptibility, presumably immunogenetic in nature. For this reason, studies have been exploring cytokine profiles, inflammatory mediators, volatile fatty acid levels, bile acid composition, and other permeability and vascular factors as putative contributors to the pathologic process.

## RISK FACTORS

Ideally, it would be helpful to know in advance which patients were at particular risk for pouchitis and which were not. The only absolute certainty in this regard is that it is patients with underlying chronic idiopathic inflammatory bowel disease who are most vulnerable; patients with familial adenomatous polyposis only rarely develop this complication.

Within the inflammatory bowel disease population, however, it is less clear what the risk factors are. Several putative markers of an immunogenetic disposition to pouchitis might include primary sclerosing cholangitis (PSC), high preoperative perinuclear anti-neutrophil cytoplasmic antibody titers, extensive backwash ileitis, and a strong preoperative history of extraintestinal complications. As with the original ulcerative colitis, smoking may exert some type of "protective" effect against pouchitis. Crohn's disease-like complications of an ileal pouch might also be anticipated in patients who had unmistakable Crohn's disease preoperatively, especially if the small bowel had been involved; but not every case of chronic refractory pouchitis, even when accompanied by granulomas or transmural inflammation, is *prima facie* evidence of preexisting Crohn's disease.

## TREATMENT

Initially, virtually all cases of pouchitis will respond favorably to treatment with metronidazole or other broad-spectrum antibiotics, including ciprofloxacin. In fact, some investigators require such a therapeutic response to be manifested before they will even accept a definitive diagnosis of pouchitis. As noted above under Natural History, all but approximately 10–15% of cases with pouchitis can be managed exclusively with antibiotic therapy, whether intermittent or chronic; the worst dilemma in managing this complication is how to treat the small but not insignificant minority of cases that are refractory to antibiotics.

In these truly refractory cases, medical treatment reflects despair more than reliable evidence. Oral and topical aminosalicylates and steroids are often used with anecdotal impressions of success; some patients seem to respond to oral anti-metabolites, but even less evidence supports the occasional resort to oral cholestyramine or topical cyclosporin, glutamine, butyrate, or Kaopectate. In any event, all such medical approaches must be disappointing to the extent that they are reminiscent of the regimens that the colectomy was designed to eliminate. A potentially more promising approach to prophylaxis against recurrent pouchitis has been suggested by Italian investigators using probiotic therapy.

As many as half the cases of chronic refractory pouchitis may ultimately come to further surgery—either pouch revision or "salvage" or complete excision with conversion to the standard Brooke ileostomy, an alternative that may have been initially less appealing to the patient, but that may ultimately restore a more acceptable quality of life.

### See Also the Following Articles

**Colectomy • Colitis, Ulcerative • Crohn's Disease • Familial Adenomatous Polyposis (FAP) • Ileoanal Pouch**

### Further Reading

Gionchetti, P., Rizzello, F., Venturi, A., Brigidi, P., Matteuzzi, D., Bazzocchi, G., Poggioli, G., Miglioli, M., and Campieri, M. (2000). Oral bacteriotherapy as maintenance treatment in patients with chronic pouchitis: A double-blind, placebo-controlled trial. *Gastroenterology* 119, 305–309.

Lohmuller, J. L., Pemberton, J. H., Dozois, R. R., Ilstrup, D., and van Heerden, J. (1990). Pouchitis and extraintestinal manifestations of inflammatory bowel disease after ileal pouch–anal anastomosis. *Ann. Surg.* 211, 622–627.

Madden, M. V., McIntyre, A. S., and Nicholls, R. J. (1994). Double-blind crossover trial of metronidazole versus placebo in chronic unremitting pouchitis. *Digest. Dis. Sci.* 39, 1193–1196.

Nicholls, R. J., and Banerjee, A. K. (1998). Pouchitis: Risk factors, etiology, and treatment. *World J. Surg.* 22, 347–351.

Phillips, S. F. (1998). Pouchitis. Up To Date, Inc. Available at http://www.uptodate.com.

Sandborn, W., McLeod, R., and Jewell, D. (2000). Pharmacotherapy for inducing and maintaining remission in pouchitis. *Cochrane Database Syst. Rev.*

Sartor, R. B. (2000). Probiotics in chronic pouchitis: Restoring luminal microbial balance. *Gastroenterology* 119, 584–587.

Shepherd, N. A., Hulten, L., Tytgat, G. N., Nicholls, R. J., Nasmyth, D. G., Hill, M. J., Fernandez, F., Gertner, D. J., Rampton, D. S., Hill, M. J., *et al.* (1989). Pouchitis. *Int. J. Colorectal Dis.* 4, 205–229.

Stahlberg, D., Gullberg, K., Liljeqvist, L., Hellers, G., and Lofberg, R. (1996). Pouchitis following pelvic pouch operation for ulcerative colitis: Incidence, cumulative risk, and risk factors. *Dis. Colon Rectum* 39, 1012–1018.

# Power Propulsion

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**manometric recording** Graphic measure of changes in pressure in localized regions of the digestive tract, indicating contractile behavior of the musculature.

**migrating motor complex** Specific pattern of small intestinal motility that begins when digestion of a meal is complete and ends with intake of the next meal; also called interdigestive motility.

**mixing movements** Specific pattern of small intestinal motility that starts with the ingestion of a meal and accomplishes mixing of the contents in the lumen; also called digestive motility.

**Power propulsion is a motility pattern that is specialized for the rapid transport of contents over long distances in the small and large intestine. It appears on mechanical records of intestinal motility (e.g., manometric recordings) as strong, long-lasting circular muscle contractions that propagate for extended distances along the bowel. These "giant" migrating contractions are considerably stronger than the circular muscle contractions that occur during the migrating motor complex or the mixing movements in the small intestine.**

## INTRODUCTION

Power propulsion, the motility pattern of giant migrating circular muscle contractions that last 18–20 seconds and span several cycles of the electrical slow waves, is a component of a highly efficient propulsive mechanism that rapidly strips the lumen clean. The propulsive movement travels at about 1 cm/sec over long lengths of intestine.

Intestinal power propulsion differs from peristaltic propulsion during the migrating motor complex and the contractions of mixing movements in that the circular contractions in the propulsive segments are stronger and propagation occurs over longer reaches of intestine. The circular contractions are not time locked to the electrical slow waves and probably reflect strong activation of the muscle by excitatory motor neurons. Power propulsion represents another of the motility programs stored in the program library of the enteric nervous system.

## PHYSIOLOGIC SIGNIFICANCE

Noxious stimulation of the mucosa starts the neural program for power propulsion in the small and large intestine. Power propulsion starts in the midjejunum and travels toward the stomach during vomiting; otherwise, the direction of travel in both the small and large intestine is in the anal direction. Abdominal cramping sensations and diarrhea are associated with power propulsion when it occurs in response to luminal events that threaten whole-body integrity. Application of irritants to the mucosa, the introduction of luminal parasites, release of enterotoxins from pathogenic bacteria, allergic reactions, and exposure to ionizing radiation all trigger the response. This suggests that power propulsion is a defense mechanism in both the upper and lower regions of the intestinal tract. It is a protective adaptation for rapid clearance of undesirable elements from the intestinal lumen. Oral clearance from the upper small intestine is achieved by vomiting of the material. Clearance from the lower intestinal tract is by way of watery feces.

Aside from its involvement in intestinal defense in potentially pathologic circumstances, operation of the power propulsion motility program also accomplishes mass movement of intraluminal material in normal states, especially in the large intestine. Mass movements in the colon following ingestion of a meal and during defecation are produced by the power propulsion program and reflect normal physiology.

### See Also the Following Articles

Basic Electrical Rhythm • Borborygmus • Colonic Motility • Migrating Motor Complex • Postprandial Motility • Small Intestinal Motility

### Further Reading

Mathias, J., and Clench, M. (1989). Alterations of small intestine motility by bacteria and their enterotoxins. *In* "Handbook of Physiology. The Gastrointestinal System I" (J. Wood, ed.). Sect. 6, Vol. 1, Pt. 2, pp. 1153–1177. American Physiological Society, Bethesda.

 

Sarna, S., and Lang, I. (1989). Motor and myoelectric activity associated with vomiting, regurgitation, and nausea. *In* "Handbook of Physiology, The Gastrointestinal System I" (J. Wood, ed.), Sect. 6, Vol. 1, Pt. 2, pp. 1179–1198. American Physiological Society, Bethesda.

Sarna, S., and Otterson, M. (1993). Myoelectric and contractile activities. *In* "Atlas of Gastrointestinal Motility in Health and Disease" (M. Schuster, ed.), pp. 3–42. Williams & Wilkins, Baltimore.

Wood, J. (1998). Enteric neuropathobiology. *In* "Functional Disorders of the Gut" (S. Phillips and D. Wingate, eds.), pp. 19–42. Churchill Livingstone, New York.

Wood, J. (2002). Neuro-pathophysiology of IBS. *J. Clin. Gastroenterol.* (in press).

Wood, J. (2003). Neurogastroenterology and digestive motility. *In* "Medical Physiology" (R. Rhoades and G. Tanner, eds.), 2nd Ed., Chap. 26, pp. 449–480. Lippincott Williams & Wilkins, Baltimore.

# Prader–Willi Syndrome

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**centromere** The site on a chromosome that pulls the chromosome toward one of the poles of the spindle during mitosis and meiosis; it is also the point of attachment of the sister chromatids.

**imprinting** A germ-line process that "presets" or predetermines the potential of a transmitted gene to be active or inactive without changing the actual sequence of the base pairs. It presumably reflects a modification of the DNA or proteins in such a way as to preset the activity of genes in the embryo.

**methylation** The process of adding a methyl group onto an existing molecule of a base pair that changes (often impedes) the ability of nuclear enzymes to "read" the genetic code.

**provocative pituitary testing** Analysis of the pituitary with specific medications previously shown to elicit a release of one or more pituitary hormones in a reproducible manner characteristic of normal or disease states.

**uniparental disomy** Two exact copies of the same chromosome or gene cluster from one parent.

**Prader–Willi syndrome is a syndrome caused by a genetic abnormality located on the long arm of chromosome 15 near the centromere. The condition is characterized mainly by hyperphagia, severe obesity, mental retardation, short stature, hypogonadism, hypotonia, behavioral abnormalities, and shortened life span if untreated. The exact cause of the condition is unknown, although abnormal hypothalamic function is thought to be a primary result of the chromosome abnormality with resultant abnormalities in growth, metabolism, and development. No cure for the condition is available. However, with early diagnosis and aggressive management of the clinical and medical problems, most of the major and life-threatening medical problems associated with this condition can be either avoided or mitigated.**

## INTRODUCTION

Prader–Willi syndrome (PWS) is the single most common genetic cause of obesity. The obesity of PWS is a consequence of both severe hyperphagia and decreased overall metabolism. However, obesity is just one component of this extremely complex condition. Overall, the condition is characterized by a constellation of neurological, autonomic nervous system, hypothalamic, endocrine, and behavioral abnormalities. Scientific and medical interest in this condition is increasing because improved understanding may lead to elucidation of the genetic influences over weight control, obesity, and obesity co-morbidities. Descriptions of PWS date as far back as the 17th century. A famous painting of Eugenia Martinez Vallejo by Juan Carreno de Miranda (*The Monstrua*) depicts a girl with the condition prior to its discovery. The first report of PWS, published in 1956 by doctors A. Prader, H. Willi, and A. Labhart, described a syndrome characterized by obesity, short stature, a severe lack of muscle tone during infancy that persists into adulthood, delayed and incomplete puberty, amenorrhea in women, hypogonadism with cryptorchidism in men, and mental retardation.

## GENETICS

PWS is seen in all ethnic and socioeconomic groups and in all countries and is equally common in females and males, with an incidence between 1:10,000 and 1:15,000. PWS is an autosomal dominant disorder caused most often (70%) by a deletion of the paternal chromosome 15 at band q11–q13. In approximately 25% of individuals, PWS is a result of maternal uniparental disomy (UPD) of chromosome 15. In this situation, two copies of the maternal chromosome are inherited with no paternal contribution. Without the presence of a chromosome donated from the father, normal imprinting on the two maternally donated chromosomes leads to the absence of gene expression in this interval. The other 5% of patients may have abnormalities in the mechanism of imprinting (leading to the absence of gene expression from the paternally donated chromosome) or translocations affecting chromosome 15q11–q13.

## CLINICAL PRESENTATION

The hallmark features of the syndrome include infant hypotonia, delayed development, childhood-onset hyperphagia and obesity, short stature, muscle hypotonia, characteristic facieses, delayed and incomplete puberty, small hands and/or feet, and mild to moderate mental retardation (IQ of 65–70). Many other important but less frequent findings have also been identified. Because there is variability among individuals with PWS, clinical diagnostic criteria (see Table I) have been established to raise diagnostic suspicion. The presence of these clinical findings is an indication for further genetic studies and genetic testing should accurately diagnosis 99% of these individuals. Since the clinical picture of an individual with PWS changes with age, the diagnostic criteria need to be considered in this context. These changes are not only important to take into account when making the diagnosis, but also in management as the co-morbidities and problems change.

In the newborn or infant, the classic presentation of PWS is profound hypotonia, lethargy, diminished deep tendon reflexes, poor feeding, below-average weight, and often a history of fetal inactivity. The infants are so "floppy" that they have little facial expression, an abnormal, weak, or absent cry, and gross motor development is delayed. The infants often experience failure to thrive because of severe feeding problems characterized by an extremely weak suck. This problem can remain severe for months and persist for years; often the severity can require special feeding interventions such as nasogastric food supplementation. Some time in the second year of life, motor function begins to improve. Gross motor skills are acquired late but by 2 years most children with PWS are walking.

In the toddler years (some time between 1 and 3 years of age), the appetite abnormalities begin to emerge. Initially, parents and health care providers are delighted to see children eat after struggling with feeding problems during the first year of life. At approximately 2 years of age, excessive weight gain is observed and later the tendency and risks for obesity become obvious as these children become more focused on food.

During the early and mid-childhood years, the physical growth abnormalities of PWS and the behavior characteristics of this syndrome begin to become apparent. There is increased body fat that is central in distribution and there is slowing of linear growth. Motor development continues to be delayed, the characteristic speech and language problems begin to emerge, and the learning disabilities are more easily identified. Growth of the PWS child begins to diverge from normal. Between 3 and 13 years of age, the 50th percentile for height corresponds to the 5th percentile in the normal population. At this point, PWS can be clearly distinguished from endogenous obesity in which the linear growth rate is accelerated and final height is normal or increased. Increased body fat and low muscle mass are also observed in PWS children. This unique pattern of growth is consistent with an abnormality in growth hormone (GH) secretion or action and studies of GH secretion have documented abnormally low GH responses to standard provocative pituitary GH stimulation testing in children and adults with PWS.

By adolescence, constant efforts to satisfy hunger result in aggressive and bizarre food-seeking activities. Hoarding food is common, as is stealing or sneaking to circumvent dietary restrictions. Complete control of the environment is needed with respect to access to food. Locks on refrigerator and cupboards are necessary and monitoring for nonfood and poisonous ingestions may be necessary. Accompanying the uncontrollable hunger is decreased calorie utilization, largely due to low muscle mass, low muscle tone, and corresponding inactivity. This contributes to the obese condition and increases the propensity for development of sleep apnea and Pickwickian syndrome.

Emotional liability and obsessive and compulsive behaviors along with intolerance to frustration are characteristic of the PWS adolescent. The obsessive–compulsive behaviors can manifest as persistent skin picking. Many adolescents with PWS develop personality problems ranging from being dull, lethargic, and indifferent to being clever, secretive, and manipulative. Transitioning from one activity to

**TABLE I Published Diagnostic Criteria for Prader–Willi Syndrome**

**Major criteria**

1. Neonatal and infantile central hypotonia with poor suck, gradually improving with age
2. Feeding problems in infancy with need for special feeding techniques and poor weight gain/failure to thrive
3. Excessive or rapid weight gain on weight-for-length chart (excessive is defined as crossing two centile channels) after 12 months but before 6 years of age; central obesity in the absence of intervention
4. Characteristic facial features with dolichocephaly in infancy, narrow face or bifrontal diameter, almond-shaped eyes, small-appearing mouth with thin upper lip, down-turned corners of the mouth (3 or more are required)
5. Hypogonadism—with any of the following, depending on age:
   a. Genital hypoplasia (male: scrotal hypoplasia, cryptorchidism, small penis and/or testes for age (< 5th percentile); female: absence or severe hypoplasia or labia minora and/or clitoris)
   b. Delayed or incomplete gonadal maturation with delayed pubertal signs in the absence of intervention after 16 years of age (male: small gonads, decreased facial and body hair, lack of voice change; female: amenorrhea/oligomenorrhea after age 16)
6. Global developmental delay in a child < 6 years of age; mild to moderate mental retardation or learning problems in older children
7. Hyperphagia/food foraging/obsession with food
8. Deletion 15q11–13 on high resolution (> 650 bands) or other cytogenetic molecular abnormality of the Prader–Willi chromosome region, including maternal disomy

**Minor criteria**

1. Decreased fetal movement or infantile lethargy or weak cry in infancy, improving with age
2. Characteristic behavior problems—temper tantrums, violent outbursts, and obsessive–compulsive behavior; tendency to be argumentative, oppositional, rigid, manipulative possessive, and stubborn; perseverating, stealing, and lying (5 or more of these symptoms required)
3. Sleep disturbance and sleep apnea
4. Short stature for genetic background by age 15 (in the absence of growth hormone intervention)
5. Hypopigmentation—fair skin and hair compared with family
6. Small hands (< 25th percentile) and/or feet (< 10th percentile) for height and age
7. Narrow hands with straight ulnar borders
8. Eye abnormalities (esotropia, myopia)
9. Thick viscous saliva with crusting at the corners of the mouth
10. Speech articulation defects
11. Skin-picking

**Supportive findings**

1. High pain threshold
2. Decreased vomiting
3. Temperature instability in infancy or altered temperature sensitivity in older children and adults
4. Scoliosis and/or kyphosis
5. Early adrenarche
6. Osteoporosis
7. Unusual skill with jigsaw puzzles
8. Normal neuromuscular studies

To Score: Major criteria are weighted at 1 point each and minor criteria are weighted at $\frac{1}{2}$ point each. Supportive findings increase the certainty of diagnosis but are not scored. For children 3 years of age or younger, 5 points are required, 4 of which should come from the major group. For children > 3 years of age and for adults, a total score of 8 is required and major criteria must comprise 5 or more points of the total score.

another is difficult and signs of depression and occasionally psychotic episodes may emerge.

At this age, the obesity will become more problematic unless dietary restrictions have been enforced. Left untreated, adolescents and adults with PWS can become morbidly obese and develop the co-morbidities of diabetes mellitus, hypertension, and cardiopulmonary insufficiency.

Physically, sexual development remains incomplete and pubertal growth is reduced. Without exogenous hormone intervention, males and females usually do not progress beyond Tanner stage II. Females may have occasional spotting but few have normal menstrual cycles. Reduced bone mineral density is typically present and this may lead to osteoporosis. These children are also at increased risk for scoliosis and/or kyphosis. In the absence of GH therapy, short stature (often severe) will be present.

The picture of PWS in the adult is dependent on the severity of the multiple problems and the intensity of

treatment during the childhood and adolescent years. Adults with PWS who have not had the benefit of early identification and treatment with specialized care (aggressive diet management, activity program, and sex steroid and growth hormone replacement) are characterized by severe obesity, decreased muscle mass, Pickwickian syndrome, sleep apnea, reduced bone mineral density, mental retardation, and behavior and psychiatric disorders. Left untreated, the life span of PWS individuals is two to three decades, with death accompanying the complications of severe weight gain including diabetes, respiratory insufficiency, and cardiac failure.

## DIAGNOSTIC TESTING

Gunay-Aygun and colleagues reviewed the sensitivity of PWS diagnostic criteria and proposed revised criteria for DNA testing. From birth to 2 years, any infant with hypotonia and poor suck should have DNA testing for PWS. From age 2 to 6 years, any child with hypotonia and a history of poor suck and global developmental delay should have DNA testing. From age 6 to 12 years, any child with a history of hypotonia and poor suck, global developmental delay, and excessive eating with central obesity should be tested for PWS. In the adult, the clinical pattern can be more varied and important historical facts may be unavailable. For adults, the authors recommend methylation testing for any individual with mental retardation, severe obesity, a history of hyperphagia, low muscle tone, hypogonadism, and short stature or adult height less than would be predicted from genetic background. Definitive diagnosis of PWS is made via methylation analysis since it detects all three groups of molecular defects described above. If methylation analysis is not available, high-resolution chromosome analysis and/or FISH (fluorescence *in situ* hybridization) can be the initial test. However, methylation analysis and (or) analysis of genomic DNA are (is) necessary to delineate the parent-of-origin for the deleted region. If biparental inheritance is identified, then PWS is ruled out. If the methylation pattern is abnormal, FISH can be used to document a deletion and/or microsatellite probes can be used to confirm maternal UPD. Abnormal methylation and negative FISH and UPD studies indicate an imprinting defect.

## TREATMENT

The treatment of PWS is a challenge given the extent of the functional and metabolic limitations associated with the condition. Since patients with PWS require a variety of interventions to optimize their health, a comprehensive plan approach is required. Although it is essential that a primary physician be identified to manage this complex problem, it is equally essential that the primary physician have available a team of experienced physicians, including those with specialties in neurology, psychiatry, urology, orthopedics, and gynecology, with other professionals from nursing, dietetics, genetics, social services, and psychology that are familiar with the PWS condition. Ancillary resources that are necessary will in part be age-dependent, but ultimately these will include social services, early intervention programs for children, physical therapy, occupational therapy, and age-appropriate educational/vocational services. A controlled and caring environment with regular routines along with pharmacological therapy may be initiated to stabilize mood and behavior and improve self-esteem. For adults, self-care has not been shown to be possible and group home environments with strict dietary controls are essential.

Since the severity of the associated health problems is directly related to the degree of obesity, nutritional intervention is the single key component of any treatment program. Appetite suppressants are ineffective in controlling overeating in individuals with PWS. Bariatric surgery has not been generally successful and can be associated with complications due to appetite abnormality and mental retardation. Weight management needs to include complete and absolute control over access to food and a calorie-restrictive diet, usually approximately 10 cal/cm of height. Dietary restrictions often need to be maintained for life in the range of 900 to 1200 kcal/day and rarely can exceed 1400 kcal/day. The low-calorie diet requires attention to the prevention of vitamin, essential fatty acid, and calcium deficiencies. Behavior modification plans that reward positive behaviors with respect to weight management and activity programs may be beneficial for some patients. Programs should also include family therapy and behavioral management components that emphasize environmental controls while simultaneously encouraging social integration and independence. Structured physical activity programs to increase energy expenditure and build muscle mass can be initiated and may sustain the individual with PWS if it is well-defined and easy to accomplish.

Endocrine abnormalities are a significant part of the medical picture of PWS. These abnormalities relate to the primary abnormalities of the hypothalamus and secondarily to the complications of the obesity and diet modifications. Pituitary function abnormalities include hypogonadotropic hypogonadism with absent, delayed, and incomplete puberty. On occasion, precocious but

incomplete puberty has been observed. GH secretion deficiency has also been documented to be part of this hypothalamic–pituitary function abnormality. Other endocrine abnormalities that have been identified include abnormalities of secretion of pancreatic secretion of insulin and pancreatic polypeptide with increased risk of diabetes. The abnormalities of glucose homeostasis and insulin secretion are not simply a consequence of the obese condition and associated insulin resistance, but have been hypothesized to be secondary to abnormalities in normal autonomic control of islet cell secretion. Thyroid deficiencies may occur in PWS individuals, although they have not been identified as common problems. PWS individuals are at high risk for osteoporosis. This can be a major problem as a consequence of the lack of spontaneous secretion of sex steroids during adolescence, growth hormone deficiency, and the dietary restrictions that limit milk and calcium intake.

Treatment of the endocrine abnormalities includes appropriately timed replacement of sex steroids. This may include human chorionic gonadotropin treatment of the infant with cryptorchidism/hypogonadism and use of estrogens and androgens at the time of adolescence. Early recognition of symptoms and signs of diabetes can allow for aggressive intervention with weight control and diet as primary treatment. Several controlled studies have now been published on the beneficial effect of GH in children with PWS and as a result GH is a Food and Drug Administration-approved therapy for growth failure in children with PWS. Daily subcutaneous administration of GH replacement (at a weekly dose of 0.24 mg/kg body weight) normalizes linear growth, promotes increases in lean body mass, decreases fat mass, and improves bone mineral density, all of which are beneficial to weight management. Therefore, growth rates of children with PWS should be monitored and referral for growth hormone evaluation is appropriate if the child's growth velocity decreases or if height is less than the third percentile. Further investigation is needed to determine whether adult GH therapy would be of benefit to the adult PWS patient.

Recent studies involving children and adults with PWS report fasting ghrelin plasma concentrations significantly higher in PWS subjects than in obese and lean control subjects. Ghrelin, a hormone predominantly secreted by the stomach, increases before every meal and decreases after nutrient intake, suggesting a role in meal initiation. Plasma ghrelin levels are also lower in obese individuals than in lean individuals. Future studies are needed regarding the role of ghrelin as an orexigenic factor driving the insatiable appetite of PWS patients and whether ghrelin antagonists could effectively reduce food intake.

As patients with PWS become older and more independent, behavioral disorders, including obsessive–compulsive disorders and psychoses, can become major issues. Serotonin-specific reuptake inhibitors may be appropriate to stabilize irritability and perseveration as initial therapies.

With appropriate intervention, the very poor clinical course can be changed for the individual with the PWS condition. Individuals who have had the benefit of early diagnosis and interventions will have more normal although generally still excessive weight, less severe shortness of stature, and persistent muscle hypotonia compared to normal, but significantly improved mobility and activity patterns than would otherwise be possible. With proper care, the behavioral problems, though significant, are manageable. The expected life spans of PWS individuals who have received anticipatory care and appropriate attention to medical problems have yet to be determined, but can be beyond 30 to 40 years and are associated with the absence of the major co-morbidities and a markedly improved quality of life.

## See Also the Following Articles

Appetite • Growth Hormone • Obesity, Treatment of

## Further Reading

Angulo, M., Castro-Magana, M., and Uy, J. (1991). Pituitary evaluation and growth hormone treatment in Prader–Willi syndrome. *J. Pediatr. Endocrinol.* 4, 167–173.

Aughton, D. J., and Cassidy, S. B. (1990). Physical features of Prader–Willi syndrome in neonates. *Am. J. Dis. Child.* 144, 1251–1254.

Butler, M. G., and Meaney, F. (1991). Standards for selected anthropometric measurements in Prader–Willi syndrome. *Pediatrics* 88, 853–860.

Carrel, A. L., Myers, S. E., Whitman, B. Y., and Allen, D. B. (1999). Growth hormone improves body composition, fat utilization, physical strength and agility, and growth in Prader–Willi syndrome: A controlled study. *J. Pediatr.* 134, 215–221.

Cassidy, S. B. (1997). Prader–Willi syndrome. *J. Med. Genet.* 34, 917–923.

Cummings, D. E., Purnell, J. Q., Frayo, R. S., Schmidova, K., Wisse, B. E., and Weigle, D. S. (2001). A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans. *Diabetes* 50, 1714–1719.

DelParigi, A. (2002). High circulating ghrelin: A potential cause for hyperphagia and obesity in Prader–Willi syndrome. *J. Clin. Endocrinol. Metab.* 87, 5461–5464.

Eiholzer, U., Nordmann, Y., l'Allemand, D., Schlumpf, M., Schmid, S., and Kromeyer-Hauschild, K. (2003). Improving body composition and physical activity in Prader–Willi syndrome. *J. Pediatr.* 142, 73–78.

Epstein, L. H., McCurley, J., Valoski, A., and Wing, R. R. (1990). Growth in obese children treated for obesity. *Am. J. Dis. Child.* 144, 1360–1364.

Gunay-Aygun, M., Schwartz, S., Heeger, S., O'Riordan, M. A., and Cassidy, S. B. (2001). The changing purpose of Prader–Willi syndrome clinical diagnostic criteria and proposed revised criteria. *Pediatrics* 108, E92.

Haqq, A. M., Farooqi, I. S., O'Rahilly, S., Stadler, D. D., Rosenfeld, R. G., Pratt, K. L., LaFranchi, S. H., and Purnell, J. Q. (2003). Serum ghrelin levels are inversely correlated with body mass index, age, and insulin concentrations in normal children and are markedly increased in Prader–Willi syndrome. *J. Clin. Endocrinol. Metab.* 88, 174–178.

Holm, V. A., Cassidy, S. B., Butler, M. G., *et al.* (1993). Prader - Willi syndrome: Consensus diagnostic criteria. *Pediatrics* 91, 398–402.

Ritzen, E. M., Lindgren, A. C., Hagenas, L., Marcus, C., Muller, J., and Blichfeldt, S. (1999). Growth hormone treatment of patients with Prader–Willi syndrome. Swedish Growth Hormone Advisory Group. *J. Pediatr. Endocrinol. Metab.* 12, 345–349.

Schuster, D., Oswei, K., and Zipf, W. B. (1996). Characterization of alterations in glucose and insulin metabolism in Prader–Willi subjects. *Metabolism* 45, 1514–1520.

Stadler, D. D. (1995). Nutritional management. *In* "Management of Prader–Willi Syndrome" (L. R. Greenswag and R. Alexander, eds.), pp. 88–114. Springer-Verlag, New York.

Whitman, B., Greenswag, L., and Boyt, M. (1998). The use and impact of psychotropic medications for managing behavior in persons with Prader–Willi syndrome. Proceedings of the 13th Annual Prader–Willi Scientific Conference, July 22, 1998, Columbus, OH.

Wren, A. M., Seal, L. J., Cohen, M. A., Brynes, A. E., Frost, G. S., Murphy, K. G., Dhillo, W. S., Ghatei, M. A., and Bloom, S. R. (2001). Ghrelin enhances appetite and increases food intake in humans. *J. Clin. Endocrinol. Metab.* 86, 5992.

# Pregnancy and Gastrointestinal Disease

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**hyperemesis gravidarum** Pernicious condition in which the pregnant patient develops severe and intractable nausea and vomiting associated with nutritional and fluid/electrolyte deficiencies.

**trimester** Portion of a pregnancy in time; first, second, and third trimesters roughly correspond to months 1–3, 4–6, and 6–9.

**The development of common gastroenterological conditions during pregnancy may present a challenge to physicians who are not familiar with the altered physiology of the gravid state. Knowledge of the most common gastrointestinal diseases in pregnancy is critical to the health of both mother and child.**

## INFLAMMATORY BOWEL DISEASE

The rates of fertility, congenital malformation, stillbirths, and spontaneous abortions in women with ulcerative colitis (UC) are comparable to those of unaffected women. Ulcerative colitis may have its onset in the first two trimesters of gestation. Women with preexisting UC and whose UC is asymptomatic in the prenatal period usually do not experience exacerbation of disease during pregnancy. On the other hand, women who have active disease before pregnancy may experience worsening of symptoms during the first trimester and significant improvement during the second trimester. Most pregnancies of women with ulcerative colitis result in delivery of normal full-term babies.

Crohn's disease is rarely diagnosed initially during pregnancy. The fertility rate in women with Crohn's disease is affected by the multiple clinical complications of the disease, such as perineal scarring, dyspareunia, and decreased libido. Women with active Crohn's disease have an increased risk for premature birth. There are no increases, however, in congenital malformations, stillbirths, or spontaneous abortions. Treatment of Crohn's disease during pregnancy with sulfasalazine, 5-aminosalicylic acid, or corticosteroids has been undertaken without risk for fetal abnormalities.

The use of immunosuppressive therapy with azathioprine or 6-mercaptopurine has generally been avoided during pregnancy, although published data have not suggested an increased risk of complications.

Immunosuppressive therapy does not represent an absolute contraindication for pregnancy or an absolute indication for termination of pregnancy.

## PANCREATITIS

The incidence of pancreatitis during pregnancy is 0.009% (less than 1 in 10,000). Approximately 90% of cases of pancreatitis during pregnancy are due to gallstones, with clinical manifestations and diagnosis similar to those in nonpregnant patients. Management should be medical, but in a setting of high-level of care. The role of endoscopic retrograde cholangiopancreatography (ERCP) in the management of gallstone pancreatitis during pregnancy is unclear and is potentially dangerous due to radiation exposure to the fetus. Surgery should be reserved for patients with life-threatening conditions.

## GALLSTONE-RELATED DISEASE

The incidence of gallstones increases in pregnancy. The prevalence in asymptomatic pregnant women is 2.5–12%. The etiology for this increased incidence is related to abnormalities in gallbladder motility, hormonal changes, cholesterol supersaturation, and changes in bile acid composition of bile.

The clinical manifestations are similar than those in nonpregnant women. Diagnosis is usually made by the use of abdominal ultrasound. Radionuclide hepatobiliary iminodiacetic acid (HIDA) scan studies are contraindicated due to radiation exposure. In patients with cholecystitis during pregnancy, conservative management with antibiotics and intravenous fluid replacement is the treatment of choice. ERCP with stone removal has been performed in a limited number of cases with extreme lead shielding and minimal use of fluoroscopy. Cholecystectomy is indicated for patients who do not respond to conservative therapy. Laparoscopic cholecystectomy is not recommended because of the high risk of damage to the gravid uterus. Open cholecystectomy during the first trimester may contribute to a risk of abortion, and surgery during the third trimester may induce labor.

## HEMORRHOIDAL DISEASE

Pregnant women commonly experience anorectal discomfort, bleeding, or anal pruritus during the third trimester of gestation. Factors commonly involved are mechanical compression of veins by the enlarging uterus and worsening constipation with increased straining during defecation. Treatment includes conservative measures such as sitz baths and suppositories. Surgical hemorrhoidectomy should be reserved for intractable cases.

## CONSTIPATION

The frequency of constipation during pregnancy is 11–40%. The pathogenesis is unclear, but may be related to increased serum progesterone levels, extrinsic compression of the colon or rectum by the gravid uterus, oral iron supplementation, and increased absorption of water and electrolytes. The management should include increased intake of fluid and dietary fiber, as well as the use of bulk-forming agents. Laxatives containing anthraquinone or cascara derivatives should not be used during pregnancy because of the potential to cause congenital malformations. Castor oil should also be avoided because it increases premature uterine contractions. The use of phenolphthalein laxatives is contraindicated during breast-feeding.

## GASTROESOPHAGEAL REFLUX DISEASE

The incidence of heartburn during pregnancy is 30–50%, and it often occurs daily. The pathogenesis of gastroesophageal reflux in pregnancy is related to the enlarging gravid uterus that causes increased intraabdominal and intragastric pressures, a hormone-mediated decrease in lower esophageal sphincter pressure, and decreased esophageal clearance. The clinical manifestations are similar to those in nonpregnant women. Esophagogastroduodenoscopy is safe during pregnancy, but is seldom needed to establish a diagnosis. The role of 24-hour pH monitoring remains to be determined. Complications of reflux such as severe erosive or ulcerated esophagitis are rarely seen.

Management includes dietary changes such as eating a diet low in fatty foods, as well as avoidance of foods with a high acidic content or substances that decrease the lower esophageal sphincter pressure, such as caffeine. Lifestyle changes such as elevation of the head of the bed and cessation of smoking are also recommended. The use of non-calcium-based antacids or sucralfate appears to be safe and effective.

Intractable gastroesophageal reflux may require the use of drugs that reduce or suppress gastric acid secretion. Cimetidine should be avoided because of antiandrogenic effects that may affect normal male fetal

development. Ranitidine use for short periods appears to be safe during pregnancy. Although certain proton pump inhibitors such as omeprazole and pantoprazole may be toxic to the fetus, lansoprazole does not appear to be toxic, at least in animals.

## NAUSEA AND HYPEREMESIS GRAVIDARUM

The incidence of nausea and emesis during pregnancy is 60–70%, and is more common in the first trimester. Hyperemesis gravidarum occurs in 0.5 to 10 of 1000 pregnancies. It presents as severe, persistent emesis that usually requires hospitalization for fluid replacement and nutritional supplementation. Hospitalization is indicated when pregnant women present with tachycardia and hypotension, ketosis, or weight loss. Associated factors include nulliparity, multiple gestations, obesity, and hydatidiform mole. Other associated factors sometimes include abnormal gastric emptying, autonomic dysfunction, hyperthyroidism, and psychological factors. Conservative management is directed to fluid and electrolyte replacement. The use of antiemetics such as metoclopramide and prochlorperazine is believed to be safe during pregnancy.

## See Also the Following Articles

**Colitis, Ulcerative • Constipation • Crohn's Disease • Gallstones, Pathophysiology of • Gastroesophageal Reflux Disease (GERD) • Hemorrhoids • Hyperemesis Gravidarum • Liver Disease, Pregnancy and • Nausea**

## Further Reading

Cappell, M. (1998). The safety and efficacy of gastrointestinal endoscopy during pregnancy. *Gastroenterol. Clin. North Am.* **27**, 37–71.

Dixon, N. P., Faddis, D. M., and Silberman, H. (1987). Aggressive management of cholecystitis during pregnancy. *Am. J. Surg.* **154**, 292–294.

Riely, C. A., and Davila, R. (2002). Pregnancy-related hepatic and gastrointestinal disorders. *In* "Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management" (M. Feldman, L. S. Friedman, and M. H. Sleisenger, eds.), 7th Ed., Vol. II, pp. 1448–1461. W. B. Saunders, Philadelphia.

Saleeby, R. G., Rosen, L., Stasik, J. J., Riether, R. D., Sheets, J., and Khubchandani, I. T. (1991). Hemorrhoidectomy during pregnancy: Risk or relief? *Dis. Colon Rectum* **34**, 260–261.

Woollson, K., Cohen, Z., and McLeod, R. S. (1990). Crohn's disease and pregnancy. *Dis. Colon Rectum* **33**, 869–873.

# Probiotics

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**prebiotic** A nondigestible food ingredient that can beneficially influence the health of the host by selectively altering the enteric flora.

**probiotic** A live microorganism that, when consumed in adequate amounts, can confer a health effect on the host.

**synbiotic** A mixture of prebiotic and probiotic elements.

**Probiotics are live microorganisms that, when consumed in sufficient amounts, can favorably influence the microbial ecology of the host and thus confer a health benefit on the host. Probiotics may exert their beneficial effects by different mechanisms, including the production of antimicrobial factors, competition for binding sites or nutrients, and modulation of the immune system.**

## TERMINOLOGY

Probiotics are biological agents, usually consumed as food supplements, that can favorably influence the microbial ecology of the host. Precise definition continues to evolve and they have recently been described as "live microorganisms which, when consumed in adequate amounts, confer a health effect on the host." The emphasis on live microbes is in contrast to prebiotics, which are nondigestible food ingredients, often of an oligo- or a polysaccharide nature, that beneficially affect the health of the host by selectively stimulating the growth or activity of certain bacterial species already established within the colon of the host. Mixtures of probiotics and prebiotics are referred to as synbiotics. Each is an example of a growing list of functional foods or neutraceuticals that confer a health benefit beyond their nutritional content. Although the term probiotic ("for life") is relatively new, the concept of consuming selected bacteria for health promotion was recognized almost a century ago. The Russian-born Nobel laureate Eli Metchnikoff regarded enteric lactobacilli and the consumption of yogurt-like foods as important for health and longevity and the French pediatrician Tissier studied enteric "bifid" bacteria in relation to diarrheal illness and suggested that they could have a therapeutic role. Probiotics are generally gram-positive bacteria and members of the genera *Lactobacillus* and *Bifidobacterium*, although other bacteria including *Escherichia coli* and nonbacterial organisms such as *Saccharomyces boulardii* have been selected as potential probiotics. Criteria for selection of microorganisms as candidate probiotics include proliferative capacity and capability of transit and survival within the gastrointestinal tract. This requires relative resistance to acid and bile. Most important are safety criteria. Lactobacilli and bifidobacteria have a long history of usage without hazard, which is the greatest testimony to their safety. In rare or exceptional circumstances, lactobacilli have been linked with systemic translocation but there appears to be no increased frequency of bacteremia with increased usage of probiotics.

## MECHANISM OF ACTION

Probiotics may exert their beneficial effects in various settings by different mechanisms. These include the production of antimicrobial factors such as bacteriocins, competitive exclusion of pathogen binding to the mucosal epithelium, competition for nutrients, conditioning of the mucosal epithelium and subepithelial structures, and modulation of the immune system. Evidence from studies *in vitro* supports each of these mechanisms. Persuasive evidence also indicates molecular signaling from commensal and probiotic organisms to the host mucosal cells. The mechanism by which the host immune system distinguishes pathogenic organisms from commensal and probiotic organisms is mediated in part by pattern recognition molecules (or toll-like receptors) on the surface of immune and epithelial mucosal cells. Ligands for these receptors include bacterial lipopolysaccharide, cell wall components, and bacterial nucleic acid.

## THERAPEUTIC APPLICATIONS

In general, the promise and claims for probiotics have outstripped the level of supporting evidence. This initially shrouded the field with a measure of skepticism that is beginning to be replaced with more rigorous

 

scientific scrutiny of the role of the enteric microflora in gastrointestinal development, physiology, and disease. The potential for therapeutic or prophylactic manipulation of the gut flora with probiotics seems most obvious in the context of gastrointestinal infections and overgrowth syndromes including antibiotic-associated overgrowth with *Clostridium difficile*. The likely participation of the commensal flora in generating cocarcinogens from dietary substrates suggests a role for probiotics in prevention of colorectal cancer. There is also persuasive evidence for a role for probiotics in food allergy and other atopic disorders. Several lines of evidence have indicated that a subset of the resident commensal flora drive the inflammatory process in patients with Crohn's disease and ulcerative colitis. This has led to the use of probiotic preparations in these conditions. Pilot studies in animal models of inflammatory bowel disease have been very encouraging and the best evidence to date for efficacy in human inflammatory bowel disease has been in patients with pouchitis following colectomy for ulcerative colitis with the creation of an ileoanal pouch anastomosis. Finally, the scope and potential of probiotics may, in the future, be redefined with the use of genetically modified organisms that are engineered for delivery of biologically relevant molecules such as regulatory cytokines, enzymes, and vaccines.

## See Also the Following Articles

**Colitis, Ulcerative • Colorectal Adenocarcinoma • Crohn's Disease • Microflora, Overview • Pharmacology, Overview**

## Further Reading

Dunne, C., and Shanahan, F. (2002). Role of probiotics in the treatment of intestinal infections and inflammation. *Curr. Opin. Gastroenterol.* 18, 40–45.

FAO/World Health Organization (2001). Report of a Joint FAO/WHO Expert Consultation: Health and nutritional properties of probiotics in food including powder milk and live lactic acid bacteria. Available at http://www.fao.org/es/ESN/Probio/report.

Shanahan, F. (2000). Probiotics in inflammatory bowel disease: Is there a scientific rationale? *Inflamm. Bowel Dis.* 6, 107–115.

# Proctitis and Proctopathy

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**diversion proctitis** Inflammation and friability of the colonic mucosa after exclusion of a distal segment of colon from the fecal stream.

**lymphoid follicular hyperplasia** Increased growth and abundance of lymphoid follicles, often seen in pathologic specimens of patients with diversion proctitis and colitis.

**mesalamine** 5-Aminosalicylic acid.

**proctitis** Inflammation of the rectum.

**proctopathy** Any pathologic process involving the rectum without having a significant component of rectal inflammation.

**short-chain fatty acids** Chemicals derived from bacterial metabolism of nonabsorbed or poorly digested dietary carbohydrates; used in enema form for diversion proctitis.

**Although the term proctitis has been applied to a number of disorders involving the rectum, its strict definition refers only to those conditions characterized by inflammation of the mucosa and/or deeper layers of the rectal wall. Other processes causing little to no rectal inflammation, such as chronic radiation injury, are served better by the term proctopathy. Some proctopathies are important clinical entities and receive a detailed discussion in this article. Rectal involvement may also be present in conditions limited to the colon, as in infectious colitis. Finally, rectal involvement may occur as a manifestation of a systemic disorder, such as amyloidosis.**

## SYMPTOMATOLOGY AND CLINICAL EVALUATION

The symptoms of proctitis and proctopathy occur due to damage of rectal mucosa and alteration of normal rectal function. Mucosal inflammation and disruption produce classic symptoms of rectal bleeding

(hematochezia), small-volume diarrhea, passage of mucus, and intermittent, crampy pain. Decreased rectal compliance results in the characteristic symptoms of increased stool frequency, urgency, painful anal spasm with limited evacuation (tenesmus), and at times, fecal incontinence. Symptoms may be exacerbated by anal involvement of the disease process. Because of the wide range of diagnoses possible with the development of the symptoms, a thorough, albeit organ-specific, history and physical examination is performed.

Pertinent information includes sexual practices, family history, prior pelvic irradiation or bowel surgeries, and a history of chronic constipation or anorectal disease. The physical examination should include an evaluation for abdominal tenderness, femoral and inguinal lymphadenopathy, and perianal ulceration, fistula, or tenderness. Rectal examination is useful for assessment of sphincter function, for the diagnosis of rectal masses, and to test for gross or occult blood. Stool cultures and tests for ova, parasites, and *Clostridium difficile* toxin are obtained when relevant. Flexible proctosigmoidoscopy and sometimes colonoscopy are used to determine the extent and severity of disease involvement, to sample colonic effluent for culture, and to obtain mucosal biopsies. Further management decisions are made based on the findings of the clinical evaluation. The etiologies of proctitis and proctopathy are shown in Table I.

## ETIOLOGIES OF PROCTITIS

### Infectious Proctitis

Sexually transmitted diseases account for most cases of infectious proctitis. Patients at highest risk include homosexual men, particularly those practicing anal receptive intercourse (ARI) and having multiple sexual partners. Patients with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) are also at high risk.

TABLE I Etiologies of Proctitis and Proctopathy

| Proctitis | Proctopathy |
|---|---|
| Infectious | Radiation |
| Bacterial | Ischemia |
| *Neisseria gonorrhoeae* | Trauma |
| *Chlamydia trachomatis* (LGV and non-LGV) | Solitary rectal ulcer syndrome |
| *Shigella* spp. | Hematologic diseases |
| *Salmonella* spp. | Lymphoma |
| *Campylobacter* spp. | Acute myelogenous leukemia |
| *Streptococcus* spp. (Group A) | Agranulocytosis |
| *Clostridium difficile* | Medullary aplasia |
| *Pleisomonas shigelloides* | Amyloidosis |
| *Mycobacterium tuberculosis* | |
| Parasitic | |
| *Treponema pallidum* | |
| *Schistosoma mansoni* | |
| *Entamoeba histolytica* | |
| Viral | |
| Cytomegalovirus | |
| Herpes simplex virus | |
| Ulcerative colitis | |
| Crohn's disease | |
| Medication-induced | |
| NSAIDs | |
| Gold | |
| Enema/suppository (bisacodyl, indomethacin, sodium phosphate, barium, hot water, acetaminophen, codeine, acetylsalicylic acid, hydrogen peroxide, vinegar, glutaraldehyde) | |
| Fecal diversion | |
| Allergy | |
| Collagen–vascular diseases | |
| Behçet's syndrome | |
| Systemic lupus erythematosus | |
| Rheumatoid arthritis | |

*Neisseria gonorrhoeae*, a gram-negative intracellular diplococcus, infects the rectum 5 to 7 days after it is transmitted by ARI or inoculation by infected vaginal fluid. The prevalence of anorectal gonorrhea may be as high as 50% in women with gonococcal pelvic inflammatory disease. Homosexual men, particularly those visiting sexually transmitted disease clinics or having genital gonorrhea, are also at high risk. Most patients have minimal symptoms, although some develop arthritis, tenosynovitis, and skin rashes as well as symptoms of proctitis. Mucosal erythema, friability, and erosions are typically seen in the anorectum on sigmoidoscopy. The presence of a mucopurulent discharge in the anal canal in a high-risk patient is very suggestive of gonococcal proctitis. Diagnosis can be obtained by performing a Gram's stain and culture of the lower rectum by either swab or rectal biopsy; repeat cultures are often necessary given the difficulty in culturing gonococcus. The treatment of gonococcal proctitis is a single dose of ceftriaxone 125 mg intramuscularly in addition to treatment for presumed concomitant chlamydial infection (see below). Alternative regimens include the use of procaine penicillin 4.8 million units intramuscularly in two doses with 1 g of probenecid given at the time of injection, tetracycline 1.5 g orally followed by 500 mg four times a day for 4 days, or spectinomycin 2 g intramuscularly.

*Chlamydia trachomatis* is characterized by lymphogranuloma venereum (LGV) and non-LGV immunotypes, both of which cause proctitis approximately 10 days after inoculation. LGV strains typically cause more severe inflammation and symptoms than non-LGV strains. Untreated LGV may mimic Crohn's disease by causing ulcerations, fistulas, abscesses, and strictures. Findings on sigmoidoscopy include mucosal granularity, erythema, and ulceration. Biopsies may show a diffuse inflammatory infiltrate with crypt abscess, granulomas, and giant cells, similar to the pathology seen in Crohn's disease. Rectal culture, either by swab or by biopsy, microimmunofluorescence antibody staining, and complement fixation testing may be helpful but are often unsuccessful in obtaining diagnostic confirmation. A single 1 g oral dose of azithromycin, 7 days of oral doxycycline, 100 mg twice daily, or 21 days of trimethoprim-sulfamethoxaxole, double-strength twice daily, are all effective treatment regimens for chlamydia proctitis. In patients with chlamydia proctitis, the empiric treatment of gonococcal proctitis even before a confirmatory diagnosis is made is recommended.

Herpes simplex virus 2 is the most common anal herpetic infection. After an incubation period of approximately 3 weeks, herpes proctitis typically lasts for 7–10 days. Perianal vesicles and ulcerations on external examination in a patient with proctitis symptoms are highly suggestive of herpes infection. Severe herpes proctitis often causes intractable pain on defecation and anal manipulation, tenesmus, pruritis, and a mucopurulent discharge. Mucosal friability, ulcerations, vesicles, and pustules are usually limited to the distal 10 cm of rectum. Sigmoidoscopy, however, can rarely be performed without significant anesthesia because of severe discomfort. Diagnosis is made from viral culture of anorectal ulcer scrapings or biopsies. Giemsa staining of material scraped from the base of ulcers or vesicles reveals the characteristic multinucleated giant cells with intranuclear inclusion bodies. Treatment consists of 10 days of oral acyclovir, 400 mg five times daily, or in cases of resistance, foscarnet. Maintenance therapy with oral acyclovir may suppress further herpes outbreaks.

Anorectal syphilis infection with *Treponema pallidum* is commonly misdiagnosed as idiopathic anal ulcers or nonspecific proctitis. Infection occurs 2 to 8 weeks after sexual transmission. Anorectal syphilis is characterized by a variety of endoscopic appearances including anal ulceration, rectal ulceration, granulomatous proctitis, and tumor-like lesions. A combination of serologic testing, dark-field examination, and immunofluorescence staining usually leads to a diagnosis. Benzathine penicillin G, 2.4 million units intramuscularly, given initially and 7 days later, is the drug of choice for anorectal syphilis. Penicillin-allergic patients should be given either tetracycline, 500 mg orally four times daily for 15 days, or erythromycin, 500 mg orally four times daily for 15 days. Patients with significant penicillin allergies typically require desensitization to penicillin.

A number of other bacterial, parasitic, and viral etiologies can cause proctitis, although they typically cause a more proximal colitis. In homosexual men, particularly those with HIV infection, proctocolitis is often caused by *Campylobacter* spp., *Shigella* spp., non-typhi *Salmonella*, *Entamoeba histolytica*, and cytomegalovirus (CMV). CMV may also cause proctitis in recipients of bone marrow transplantation or chemotherapy. In Third World countries, tuberculosis is an often unrecognized cause of anorectal abscess and fistula and may occur in the absence of pulmonary infection. Cases of proctitis caused by *Pleisomonas shigelloides*, group A *Streptococcus*, and *Schistosoma mansoni* have been reported in the literature, mainly in homosexual men.

## Ulcerative Proctitis

Ulcerative proctitis, a chronic inflammatory process limited to the rectum, affects approximately one-third to

one-half of patients diagnosed with ulcerative colitis. Although patients with ulcerative proctitis generally follow a more benign course with fewer symptoms than those with ulcerative colitis, 30–50% of them will develop more proximal disease distal to the splenic flexure within 10 years. The 10-year survival rate for ulcerative proctitis is high, almost 98% in one series. Annual incidence rates of ulcerative proctitis show that males are more likely to develop the disease and the disease is more common in urban than rural areas. The pathophysiology is similar to that of ulcerative colitis. Patients present with typical proctitis symptoms such as rectal bleeding, pain, and tenesmus. Endoscopic findings in the rectum include loss of vascular pattern, erythema, granularity, and friability of the mucosa. Crypt abscess formation, crypt architectural distortion, and a polymorphonuclear cell infiltrate in the lamina propria are the most common histopathologic findings.

Excellent treatments exist once the diagnosis of ulcerative proctitis is made. The initial goal of therapy is to induce remission. Mesalamine suppositories and enemas have been shown to be superior to oral mesalamine and steroid-based topical treatments in inducing remission after 2–4 weeks of therapy. Optimal doses for inducing remission range from 0.5 to 1.5 g of topical mesalamine per day. Once clinical remission is obtained, the treatments are focused on the maintenance of remission. Mesalamine suppositories and oral 5-aminosalicylic acid (5-ASA) maintain 1 year remission at similar rates, between 60 and 90%.

### Crohn's Proctitis

Crohn's proctitis without colitis or perianal disease is extremely rare. 5-ASA suppositories or enemas, effective in ulcerative proctitis, have not been well studied in Crohn's proctitis but are often given due to lack of alternative therapies.

### Medications

Many pharmacological agents can cause colitis, but only a few may affect the rectum without other gastrointestinal involvement (Table 1). Nonsteroidal anti-inflammatory drugs (NSAIDs) are likely the most common cause of drug-induced proctitis, particularly if given in an enema form. Other enemas and suppositories can cause rectal inflammation from either local mucosal injury or pressure-induced injury. Treatments with gold for rheumatoid arthritis rarely lead to enterocolitis and/or ulcerative proctitis. Discontinuation of the offending agent is the most important intervention for these conditions.

### Diversion Proctitis

Diversion colitis or proctitis is characterized by inflammation and friability of the colonic mucosa after exclusion of a distal segment of colon from the fecal stream. As early as 1 month after surgery, almost all excluded segments will have some degree of endoscopic or histologic abnormality. Histopathologic changes, including mucosal fissures, granulomas, crypt abscesses, architectural distortion, and transmural inflammation, can mimic changes seen in patients with inflammatory bowel disease. Lymphoid follicular hyperplasia, however, may be a distinctive feature of diversion colitis. The diagnosis is often confirmed when mucosal changes resolve after restoration of the fecal stream, although mucosal abnormalities persist in approximately 50% of cases. Short-chain fatty acids, important nutritional substrates for the colonic epithelium, are effective in the treatment of diversion proctitis when given locally as enemas.

### Allergic Proctitis

Allergic proctitis is typically seen in infants who are sensitive to cow's milk protein or soy protein. Signs and symptoms vary from the presence of occult gastrointestinal blood loss to frank hematochezia and diarrhea. Other foods, such as egg white, peanuts, nuts, or fish, have also been implicated in patients with allergic gastroenteropathy and uncommonly in patients with allergic proctitis. Endoscopic findings of allergic proctitis are nonspecific, but rectal biopsy characteristically reveals eosinophilic infiltration within the lamina propria and intraepithelial eosinophils in surface and crypt epithelium. Treatment primarily involves elimination of the potential allergen and occasionally requires the use of corticosteroids.

### Collagen Vascular Disease

A number of rheumatologic diseases can affect the gastrointestinal tract by autoimmune mechanisms, systemic inflammation, or vasculitis. Proctitis from these diseases is rare. Behçet's disease and systemic lupus erythematosus have been reported as causing proctitis. Rectal biopsies in patients with rheumatoid arthritis may reveal evidence of chronic inflammation and vasculitis. It is a generally accepted principle that anti-inflammatory and immune therapy directed at the systemic disease will improve accompanying gastrointestinal manifestations.

## ETIOLOGIES OF PROCTOPATHY

### Radiation Proctopathy

Radiation proctopathy commonly occurs after radiation therapy for the treatment of pelvic malignancies. Prostate, cervical, uterine, bladder, testicular, and rectal cancers are among the most common malignancies treated with radiation. A large discrepancy exists in the literature regarding the prevalence of radiation proctopathy in patients receiving pelvic radiation, with ranges between 5 and 80%. A dose of 65–70 Gy of external beam radiation is typically required to cause radiation proctopathy. Acute radiation proctopathy occurs in approximately one-third of patients and is characterized by diarrhea, urgency, and tenesmus, usually without hematochezia. Chronic radiation proctopathy occurring 6–12 months after radiation therapy is often characterized by rectal bleeding due to rupture of telengiectasias or oozing from friable, ischemic mucosa. Functional symptoms, such as difficulty with evacuation, fecal urgency and incontinence, small-volume diarrhea, and rectal pain, are not uncommon and can lead to significant morbidity.

Because of the lack of randomized controlled clinical trials, effective treatments for radiation proctopathy are often given empirically without significant supportive evidence. Generally, bleeding is best treated endoscopically, but it may respond to various pharmacotherapies. Noncontact methods of endoscopic therapy, such as laser and argon plasma coagulation, are typically more effective than contact methods, such as heater probe and bipolar electrocautery, in the obliteration of bleeding telengiectasias. Sucralfate, in oral and enema form, and topical 4% formalin applied endoscopically appear to be more effective than aminosalicylate or corticosteroid enemas in treating hemorrhagic radiation proctitis, although no direct comparisons have been performed in clinical trials. Less well-studied treatments include short-chain fatty acid enemas, misoprostol enemas, hyperbaric oxygen therapy, vitamins C and E, oral estrogen/progesterone, and oral sodium pentosan polysulfate. Vitamin A was recently found to be highly effective in one patient who developed a symptomatic radiation-induced anal ulcer. Unfortunately, because functional radiation proctopathy is poorly studied, it is unclear whether or not any of the treatments mentioned are effective.

### Ischemic Proctopathy

Because of the extensive network of vascular collaterals supplying the rectum, ischemic proctopathy is rare. Ischemic proctopathy usually results from a sudden, major interruption in blood flow, such as that occurring after aortoiliac surgery. However, severe atheromatous disease combined with systemic hypotension may also compromise the otherwise abundant blood supply to the rectum. Diarrhea, abdominal pain, and unexplained sepsis in the first few days after an aortic operation are warning signs of intestinal ischemia. A sigmoidoscopy with biopsy confirms ischemic changes in the rectum, such as mucosal ulcerations and capillary dilation in overlying granulation tissue. Mild cases may be treated conservatively and are likely to resolve with hemodynamic support. The treatment of intractable rectal bleeding due to ischemic proctopathy usually requires surgical diversion, although endoscopic coagulation and local treatments such as formalin instillation have been reported.

### Traumatic Proctopathy

Patients participating in ARI or, more commonly, in sexual practices involving the insertion of foreign bodies or various body parts (fists, forearms, etc.) into the anorectum may develop traumatic proctopathy. This etiology likely represents a pathophysiologic spectrum of rectal injury, from benign mucosal tearing to severe ischemia and/or perforation. If the sexual practice is found to be the cause of proctopathy, the physician must warn the patient about the risk of foreign body impaction and/or perforation and recommend that the behavior be discontinued. If an object is impacted in the rectum and cannot be retrieved at the bedside, it is removed in the operating room under general anesthesia.

### Solitary Rectal Ulcer Syndrome

This poorly understood condition is seen in patients with chronic straining, rectal prolapse, and nonrelaxation of pelvic musculature with defecation. It is characterized by the presence of a large ulcer or multiple ulcers 4 to 15 cm from the anal verge. Solitary rectal ulcer syndrome may be mistaken for inflammatory bowel disease by inexperienced clinicians. Histologic features include fibromuscular proliferation in the lamina propria and glandular crypt distortion. Treatment with fiber, stool softeners, and biofeedback is generally preferable to surgical management.

### Hematologic Diseases

Gastrointestinal involvement may occur in a variety of hematologic diseases. The anorectum alone is rarely involved. In a series of 514 patients hospitalized for miscellaneous hematologic diseases, anal lesions, such as infiltration and ulceration, were seen most

commonly in patients with agranulocytosis, medullary aplasia, or acute myeloid leukemia. Treatment included chemotherapy or surgical drainage when an abscess was present. Anorectal infiltration with lymphoma is uncommon but is an AIDS-defining illness in patients with HIV infection.

## Amyloidosis

Amyloid protein often infiltrates the rectum and can be detected on submucosal rectal biopsies performed to diagnose systemic amyloidosis. Although gastrointestinal amyloidosis can cause chronic constipation, diarrhea, and malabsorption, rectal amyloid infiltration rarely leads to clinical manifestations associated with proctopathy.

## See Also the Following Articles

**Amyloidosis • Colitis, Ulcerative • Cow Milk Protein Allergy • Diarrhea, Infectious • Foreign Bodies • Sexually Transmitted Diseases • Solitary Rectal Ulcer Syndrome**

## Further Reading

Cohen, R. D., Woseth, D. M., Thisted, R. A., *et al.* (2000). A meta-analysis and overview of the literature on treatment options for left-sided ulcerative colitis and ulcerative proctitis. *Am. J. Gastroenterol.* 95, 1263–1276.

Corman, M. L. (1998). "Colon and Rectal Surgery." 4th Ed. Lippincott Williams & Wilkins, Philadelphia, PA.

Goldman, H., and Proujansky, R. (1986). Allergic proctitis and gastroenteritis in children: Clinical and mucosal biopsy features in 53 cases. *Am. J. Surg. Pathol.* 10, 75–86.

Guillemot, F., Colombel, J. F., Neut, C., *et al.* (1991). Treatment of diversion colitis by short-chain-fatty acids. Prospective and double blind study. *Dis. Colon Rectum* 34, 861–864.

Hong, J. J., Park, W., and Ehrenpreis, E. D. (2001). Review article: Current therapeutic options for radiation proctopathy. *Aliment. Pharm. Ther.* 15, 1253–1262.

Ilnyckyj, A. (2001). Clinical evaluation and management of acute infectious diarrhea in adults. *Gastroenterol. Clin. North Am.* 30, 599–609.

Meucci, G., Vecchi, M., Astegiano, M., *et al.* (2000). The natural history of ulcerative proctitis: A multicenter, retrospective study (GSMII). *Am. J. Gastroenterol.* 95, 469–473.

Nelson, R. L., and Schuler, J. J. (1982). Ischemic proctitis. *Surg. Gynecol. Obstet.* 154, 27–33.

Pare, A. A., and Gottesman, L. (1997). HIV infection and the gastrointestinal tract: Anorectal diseases. *Gastroenterol. Clin. North Am.* 26, 367–377.

Parsons, D. P., and Isler, J. T. (1999). Office management of common anorectal problems: Approach to the patient. *Primary Care Clin. Office Pract.* 26, 15–35.

Tjandra, J. J., Fasio, V. W., Church, J. M., *et al.* (1992). Clinical conundrum of solitary rectal ulcer. *Dis. Colon Rectum* 35, 227–234.

# Protein-Calorie Deficiency—"Kwashiorkor"

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**cachexia** Severe wasting associated with a low serum albumin; due to excess cytokine production.

**kwashiorkor** Selective protein-calorie malnutrition with edema and a fatty liver.

**marasmus** Generalized starvation with loss of body fat and protein.

**protein-calorie deficiency** Occurs either because of deficient protein intake (undernutrition) or because of a relative excess of calorie intake (overnutrition).

**sarcopenia** Loss of lean body mass associated with the aging process.

**undernutrition** Defined by one or more of the following conditions: (a) unintentional loss of > 10% of usual body weight in the preceding 3 months, (b) body weight <90% of ideal for height, or (c) body mass index < 18.5. Body weight <90% of ideal body weight for height represents a risk of malnutrition, <85% of ideal body weight represents malnutrition, <70% of ideal body weight constitutes severe malnutrition, and <60% of ideal body weight is not compatible with life.

**Kwashiorkor and marasmus are usually regarded as the extremes of a continuum encompassing protein-calorie malnutrition. Severe protein-energy malnutrition is a leading cause of death in children younger than 5 years of age. Ten to 20% of children die when admitted to the hospital with the diagnosis of kwashiorkor, the highest mortality of any pediatric disease. Protein-calorie malnutrition occurs in infants and children in the developing nations, but it is also reported in older adults and can occur in any country of the world. The prevalence of malnutrition varies in older people; it occurs in 1–15% of ambulatory outpatients, 25–65% of long-term care residents, and 35–65% of hospitalized patients. Malnutrition has been associated with increased mortality, morbidity, and prolongation of hospitalization. It also results in loss of function and adversely affects the quality of life.**

## INTRODUCTION

Dr. Cecily William first described kwashiorkor in 1935 in the natives of the Krobo Ga-Adangbe megatribe of South Eastern Ghana. The word "kwashiorkor" (the pronunciation in Krobo is *kwasiorkor*, there being no "sh" in the alphabet) primarily translates to "the disease suffered by the child displaced from the breast." The weaned child is fed a thin gruel of poor nutritional quality or diluted baby formula (compared with mother's milk) and fails to thrive. A child with kwashiorkor tends to be older than one with marasmus and tends to develop the disease after weaning. The marasmic children are associated with early abandonment or failure of breast-feeding and with consequent infections such as gastroenteritis. Such infections result from the improper hygiene and inadequate knowledge of rearing that are often seen in slums in developing nations.

It is said that childhood undernutrition in the developing world represents the final common pathway for the expression of illiteracy, inadequate sanitation, insufficient access to medical care, poverty, poor personal hygiene, overcrowding, poor crop management, droughts, and insufficient or inappropriate use of the available resources. These factors act at national, regional, and village levels as well as at individual family levels. Kwashiorkor has been seen even in developed nations and usually results from poverty, poor nutritional information (restricting milk or formula simply because of parent or child preference, excessive dilution of milk, substituting formula with nondairy creamer, prolonging a liquid diet after hospitalization for gastroenteritis, or eliminating milk from the child's diet), presumed food allergy with avoidance of certain foods, use of diets deficient in proteins, pure vegetarian diets, and, most importantly, poor feeding skills. Chronic malabsorption, resulting from conditions such as cystic fibrosis, is the main cause of protein-calorie deficiency in children in the United States. In developed countries, most protein-calorie malnutrition is seen in older persons with cancer and in patients with HIV infection.

## CLASSIFICATION

Clinically, protein-calorie malnutrition has three forms:

1. Marasmus (dry) is the most common form of protein-energy malnutrition in most developing

 

nations. It results from near starvation with deficiency of protein and nonprotein nutrients. The marasmic child consumes less than adequate amounts of food, often because the mother is unable to breast-feed, resulting in loss of fat, loss of muscle mass, and thin appearance.
2. Kwashiorkor (wet) is less common and is usually manifested as marasmic kwashiorkor. It is associated with a low serum albumin and edema.
3. The combined form is marasmic kwashiorkor. Children with this form have some edema and more fat compared to those with marasmus.

## PATHOPHYSIOLOGY

Weight loss occurs when there is insufficient intake or absorption of dietary calories and/or increased expenditure of energy compared with daily requirements, and/or increased catabolism, leading to loss of body fat and protein. The healthy human body is composed of fat-free mass (FFM) and body cell mass (BCM). The FFM is composed of extracellular and intracellular water, the bony skeleton, and visceral protein, whereas the BCM is composed of intracellular water, body fat, and energy reserves in the form of intracellular glycogen and proteins. The human body stores between 15 and 25% of its energy as fat, which is greater in women than in men and is available for the production of endogenous fatty acids during starvation. The expenditure of body stores of energy is different in starvation and stress. In starvation, there is a decrease in the size of all body compartments, whereas stress reduces the BCM, increases intracellular water, and has variable effects on body fat. Weight loss is slowed by reducing the metabolic rate of the active tissues, largely the result of loss of some of the body's protein. Such a protein-depleted body requires less dietary protein for maintenance. Muscle proteins are responsible for most of the protein losses, compared to central lean tissues (liver, gastrointestinal tract, kidney, blood cells, and immune cells), which are relatively spared. Most of the physiologic functions and homeostasis are maintained, so long as the starvation energy ration is not too low, allowing for normal adaptation. The clinical consequences of this adaptation are reduced muscle mass (cardiac, respiratory), muscle weakness and functional disability, reduced cardiac and respiratory capacity, mild hypothermia, anemia, and reduced protein reserve.

Patients with severe tissue injury commonly develop systemic inflammatory response syndrome (SIRS), a hypermetabolic response. SIRS is defined as the presence of two or more of the following symptoms: fever (or profound hypothermia), tachycardia, tachypnea, and leukocytosis. Other features include changes in acute-phase serum protein concentration, increased energy expenditure, increased whole-body protein turnover, anorexia, and protein wasting. Similarly, cachexia, or cytokine-induced malnutrition, is seen in patients with inflammatory diseases or malignancy associated with continued weight loss. Classic features include changes in acute-phase serum proteins, (e.g., increased C-reactive protein, fibrinogen, and ferritin, and decreased transferrin, prealbumin, and albumin), the anemia of chronic inflammation, anorexia, and the partial nullification of a previously successful adaptation to starvation. Protein-calorie malnutrition is increasingly recognized as contributing to the protein wasting associated with organ failure in conditions such as chronic renal failure and end-stage heart disease. Protein catabolism is responsible for SIRS, whereas decreased food is the major reason for lean tissue loss in the cachectic syndromes.

## ETIOLOGY OF PROTEIN-CALORIE DEFICIENCY

Initially, it was thought that kwashiorkor was due to protein deficiency in the absence of adequate energy intake. However, a number of investigators reported no differences in the nutritional backgrounds of people with kwashiorkor and those with marasmus. This resulted in alternative theories explaining the pathogenesis of kwashiorkor, such as the concept of failed adaptation, which posits that some children adapt appropriately (marasmus) to protein-calorie deficiency whereas others do not (kwashiorkor). In addition, some toxins or nutritional factors have been proposed as etiologic factors, including free radicals, aflatoxins, leukotrienes, essential fatty acids, and zinc deficiency. Mild chronic infection is common in children with kwashiorkor and thus the cytokine excess may result in extravasations of albumin from the intravascular space, producing hypoalbuminemia and edema.

Development of malnutrition is attributed to a number of risk factors, including social and psychological status, diseases producing anorexia or malabsorption, and diseases producing hypermetabolism. These risk factors can easily be remembered by using the mnemonic "Meals on wheels" (Table 1). Poor, older adults are especially at increased risk of malnutrition if they live in neighborhoods with high crime rates. Such older adults, fearing for their safety, remain homebound, which limits their ability to shop and thus restricts their chances of optimal nutrition. Older adults

TABLE I Meals on Wheels Acronym: Common Risk Factors for Undernutrition

| |
|---|
| Medications (polypharmacy, herbal preparations) |
| Emotional causes (dysphoria, depression, psychosis) |
| Appetite disorders (anorexia tardive, abnormal eating attitudes, alcholism, abuse) |
| Late-life paranoia |
| Swallowing disorders (dysphagia) |
| Oral factors (tooth loss, periodontal infection, gingivitis, poorly fitted dentures) |
| No money (poverty), nosocomial infection (tuberculosis, chronic intestinal parasites, *Clostridium difficile*) |
| Wandering (dementia) |
| Hyperactivity/hypermetabolism (tremors, movement disorders, thyrotoxicosis, Addison's disease, pheochromocytoma) |
| Enteral disorders (chronic diarrhea, malabsorption syndromes) |
| Eating problems (altered food preferences, decreased taste and flavor perception) |
| Low-nutrient diets (low salt, low cholesterol, antidiabetic, fad diets, dilution of baby formula) |
| Shopping and food preparation problems (impaired mobility, unsafe environment, inadequate transportation), stones (cholelithiasis) |

are further at risk if they have chronic medical conditions (e.g., Parkinson's disease, chronic obstructive pulmonary disease, heart failure, depression, gallstones, hyperthyroidism, hypercalcemia, pheochromocytoma, cancer, and hypoadrenalism). These conditions are complicated by the anorexia of aging, which is often multifactorial, encompassing age-related changes in appetite regulation, systemic diseases, iatrogenesis, and psychological factors. In young children, poverty and ignorance are the major causes of protein-calorie deficiency, and in young adults, AIDS has become the major cause of undernutrition, but in older adults, depression appears to be the major cause. In older men, testosterone deficiency and lack of physical activity are important causes of loss of lean body mass (sarcopenia).

## CLINICAL EVALUATION OF PATIENTS

### History

In evaluating patients, a history should be obtained from the parents, social workers, and caregivers and medical records should be reviewed. Identification of risk factors will help direct further questioning concerning functional and socioeconomic conditions. A review should include questions about diet habits and dietary restrictions (including those imposed by the patient or parents), religious and cultural beliefs, and use of special diets (heart-healthy, low-cholesterol, renal, diabetic or low-salt diets). Alcoholism is not a rare condition in older adults and should be screened for using the CAGE or Michigan Alcoholism Screening Test (MAST) tools. A history of mouth problems in the older population should be obtained, and referral made to a dentist, if required. A review of medications that can cause anorexia and weight loss is mandatory. These will include cardiovascular drugs (e.g., digoxin, amiodarone, procainamide, quinidine, spironolactone), psychiatric drugs (e.g., phenothiazines, lithium, selective serotonin reuptake inhibitors, tricyclic antidepressants), antiinfective drugs, antineoplastics, antirheumatics, drugs causing malabsorption (e.g., laxatives, cholestyramine, methotrexate), and agents increasing metabolism (e.g., theophylline, thyroid extract, L-thyroxine).

Adults should be screened for depression by history. The degree of symptomatology can be followed using either the Beck Depression Inventory or the Geriatric Depression Scale. Screening tools for dementia are available (e.g., Mini Mental Status Exam or Saint Louis University Mental Status Exam) and can be used if indicated. The Mini Nutritional Assessment (MNA) is a validated tool with a positive predictive value for detecting undernutrition of 97% in older community-dwelling adults. The sensitivity and specificity of this tool are 96 and 98%, respectively. SCALES (an acronym for sadness, cholesterol, albumin, loss of weight, eating problems, and shopping and cooking problems), a well-validated, highly sensitive tool that is simple to administer by nonmedical professionals, can be used in various clinical settings and does not require sophisticated physical examination. The Subjective Global Assessment (SGA) incorporates functional capacity as an indicator of malnutrition and relies mainly on physical signs of malnutrition and malnutrition-inducing conditions. SGA is a validated tool for prognosis (but not nutritional status) in hospitalized patients, with a sensitivity of 82% and specificity of 72%.

### Physical Examination

A careful physical examination can characterize and define the extent of malnutrition. Measurements of unclothed weight and height are essential for establishing the severity of malnutrition in all patients, but may be confounded by the effect of edema and ascites. Different classifications, used to determine childhood nutritional status, include those of Gomez, Wellcome, and Waterlow.

## Anthropometry

Measurements of subcutaneous fat and skeletal muscle can help to determine the severity of protein-calorie deficiency. Specialized calipers and a tape measure are used to estimate body fat from the thickness of the skin fold of the posterior mid-upper arm. This measurement is not routinely available, and requires some operator experience for accuracy. Table II indicates the severity of malnutrition in children with various upper arm circumferences. More sophisticated tools are available, such as B-mode ultrasound, bioelectrical impedance, underwater weighing, computed tomography, magnetic resonance imaging, and dual-photon absorptiometry. These tests require specialized equipment and are very costly.

## Physical Findings

A child with kwashiorkor is characterized by marked muscle atrophy with normal or increased body fat, and anorexia is almost universal. On the other hand, children with marasmus are characterized by wasting of muscle mass and depletion of fat stores. Classically, children have severe constipation and are voraciously hungry. Weight loss can be recognized by decreased temporal and proximal extremity muscle mass, by decreased skin fold thickness, or by a "pinch test," especially in younger adults. Tables III and IV show the clinical findings seen in patients with protein-calorie deficiency.

## Laboratory Assessment

Selected laboratory tests, most of which are widely available, are used to characterize and quantify malnutrition. However, recent data showing that most of these tests are altered by cytokine release bring into doubt their specificity and value in quantifying undernutrition.

### *Serum Proteins*

Serum albumin, with a half-life of 2–3 weeks, is a sensitive but nonspecific measure of protein-calorie deficiency. The serum albumin level should be interpreted in the clinical setting, because it can decrease with rapid fluid shifts (as seen in acute trauma, sepsis, or acute inflammation), cirrhosis of liver, AIDS, cancer, inflammatory bowel disease, and nephrotic syndrome. Tumor necrosis factor α, interleukin-2 (IL-2), and IL-6 inhibit the synthesis of albumin and produce extravasation of albumin into the extravascular space. Several serum proteins with short half-lives are also used to measure protein-calorie deficiency; these include transferrin (half-life 9 days), prealbumin (half-life 2 days), retinol binding protein (half-life 12 hours), insulin growth factor (half-life 2–4 hours), fibronectin (half-life 4 hours), and C-reactive protein (half-life 4–6 hours). However, levels of these proteins should be interpreted with caution, because they are affected by shifts in extracellular volume that occur in acute and chronic illnesses.

TABLE II Mid-Upper-Arm Circumference in Children Aged 1–5 Years

| Circumference | Level of nutrition |
|---|---|
| >14 cm | Normal |
| 12.5–14 cm | Mild/moderate malnutrition |
| <12.5 cm | Severe malnutrition |

TABLE III Physical Examination Findings

| Kwashiorkor | Marasmus |
|---|---|
| Normal or nearly normal weight and height for age | Diminished weight and height for age |
| Anasarca | Emaciated and weak appearance |
| Moon face (rounded prominence of the cheeks) | Bradycardia, hypotension, and hypothermia |
| Pursed appearance of mouth | Thin, dry skin |
| Pitting edema in the lower extremities and periorbitally | Redundant skin folds caused by loss of subcutaneous fat |
| Dry, atrophic, peeling skin with confluent areas of hyperkeratosis and hyperpigmentation | Thin, sparse hair that is easily plucked |
| Dry, dull, hypopigmented hair that falls out or is easily plucked | |
| Hepatomegaly (fatty liver infiltrates) | |
| Distended abdomen with dilated intestinal loops | |

### *Serum Cholesterol*

Serum cholesterol levels lower than 160 mg/dl have been considered a reflection of low lipoprotein and thus of accompanying protein levels. Hypocholesterolemia seems to occur in the late stages of malnutrition, limiting its ability as a screening tool, but it is a useful prognostic indicator. Like serum proteins, its plasma concentration is altered by excess cytokine production.

TABLE IV Physical Findings of Vitamin and Mineral Deficiencies Associated with Protein-Calorie Malnutrition

| Deficiency | Findings |
|---|---|
| Vitamin A | Dry conjunctiva, corneal ulceration, "goose bumps" |
| Thiamine ($B_1$) | Opthalmoplegia, congenital hepatic fibrosis, hyoreflexia, confabulation, cerebellar gait, past pointing |
| Riboflavin ($B_2$) | Angular stomatitis, cheilosis |
| Pyridoxine ($B_6$) | Peripheral neuropathy |
| Cobalamin ($B_{12}$) | Optic neuritis, loss of vibratory and position sense |
| Vitamin C | Gingival hypertrophy, easy bruising, perifollicular hemorrhage |
| Vitamin D | Osteomalacia, muscular hypotonia |
| Vitamin K | Hemorrhages |
| Niacin | Dermatitis (hyperpigmentation of sun-exposed areas), diarrhea, dementia, and sometimes death |
| Zinc | Diminished taste, "flaky rash" on lower extremities |

### *Immune Function*

There is mounting evidence that the T lymphocyte count is a useful indicator of nutritional status and outcome. A decrease in total lymphocytes (TLCs) to less than 800/μl reflects severe undernutrition. Undernutrition can also lead to suppression of cellular immunity, manifested by the delayed hypersensitivity reaction. Undernutrition in both young children and older adults results in a marked decrease in CD4+ T cells.

## TREATMENT

The guideline for the management of severely malnourished children developed by the World health Organization (WHO) consists of three phases: initial treatment, rehabilitation, and followup. The initial phase is critical, with special emphasis on treating hypoglycemia, hypothermia, infection, and dehydration. Electrolyte and vitamin deficiencies are treated in the initial phase, and treatment is extended to the rehabilitation phase, with the exception that iron is given only in the later phase. Feeding is started in the initial phase but is advanced after the second week in the rehabilitation phase. The rehabilitation phase lasts approximately 2–6 weeks. During this phase, the mother is trained to continue care at home and socioeconomic problems are addressed. In the followup phase, physical, emotional, and mental health issues are monitored and addressed and appropriately treated. It needs to be recognized that prevention by providing adequate food resources, nutritional education, and vaccinations to prevent common diseases are far more cost-effective compared to treating malnutrition in children after it occurs.

In adults, the initial step in treatment of undernutrition is the search for treatable causes. Caloric supplements, when used, should be given between meals and not with them. In some cases, the use of orexigenic drugs such as megestrol or medroxyprogesterone and/or dronabinol (tetrahydrocannibinol) may be useful.

## See Also the Following Articles

**Malnutrition • Nutrition Assessment • Nutrition in Aging • Pancreas, Nutritional Effects on the**

## Further Reading

Liu, T., Howard, R. M., Mancini, A. J., and Weston, W. L. (2001). Kwashiorkor in the United States: Fad diets, perceived and true milk allergy, and nutritional ignorance. *Arch. Dermatol.* 137(5), 630–636.

Morely, J. E. (2003). Anorexia and weight loss in older persons. *J. Gerontol. Med. Sci.* 58A(2), 131–137.

Ogden, C. L., Kuczmarski, R. J., Flegal, K. M., and Mei, Z. (2002). Centers for Disease Control and Prevention 2000 growth charts for the United States: Improvement to the 1997 National Center for Health Statistics version. *Pediatrics* 109(1), 45–60.

Omran, M. L., and Morley, J. E. (2000). Assessment of protein energy malnutrition in older persons, Part I: History, examination, body composition, and screening tools. *Nutrition* 16(1), 50–63.

Omran, M. L., and Morley, J. E. (2000). Assessment of protein energy malnutrition in older persons, Part II: Laboratory evaluation. *Nutrition* 16(2), 131–140.

Williams, C. D. (1935). Kwashiorkor: A nutritional disease of children associated with maize diet. *Lancet* ii, 1151–1152.

William, C. D. (1933). A nutritional disease of childhood associated with a maize diet. *Arch. Dis. Child.* 8, 423–428.

# Protein Digestion and Absorption of Amino Acids and Peptides

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**oligopeptide** An oligomer of amino acid units joined by peptide linkages. The term "oligopeptide" is commonly used to refer to structures containing 4 to 25 amino acid residues.

**peptide bond** The covalent chemical bond between two amino acid residues. It is formed by the subtraction of a water molecule from the amino group attached to the α-carbon of one amino acid and the carboxy group attached to the α-carbon of a second amino acid residue.

**protein** A macromolecular complex containing a large number of amino acid residues joined to one another via peptide bonds. Proteins may, in addition to the 20 different amino acids that they generally are made up of, contain various amino acid residues that have been modified posttranslationally by phosphorylation, hydroxylation, glycosylation, or attachment of fatty acid residues.

**The dietary intake of proteins varies considerably with the nature of the diet and the main protein sources in the diet (plant versus animal origin). However, in almost all developed countries, the average protein intake is approximately 100 g/day. In addition, almost 60 g of endogenous proteins from gastrointestinal secretions and saliva enters the small intestine so that a total of approximately 160 g of protein per day undergoes hydrolysis by gastric, pancreatic, and brush border membrane-bound proteases and peptidases. The end products are absorbed by multiple transport systems in the apical membrane of the epithelial cells.**

## HYDROLYSIS OF PROTEINS AND DETERMINANTS OF THEIR DIGESTABILITY

The lumenal and brush border-bound digestive enzymes initially release a vast spectrum of medium-sized and short-chain peptides and eventually free amino acids. Although most proteins and oligopeptides are rapidly degraded, some structures are fairly resistant to hydrolysis. In particular, glycosylated peptides and those containing multiple prolyl residues are more stable against attack by proteases and peptidases. This intrinsic proteolytic stability is of particular importance for understanding the "survival" of the immunodominant epitopes from α-gliadin that account for the stimulatory activity of dietary gluten on intestinal and peripheral T lymphocytes in patients with celiac disease. The α-gliadin peptides are rich in proline and glutamine residues, which are exceptionally resistant to enzymatic processing. The very low activity of dipeptidyl peptidase IV and dipeptidyl carboxypeptidase I in the gastrointestinal tract determine as rate-limiting enzymes the digestive breakdown of these peptides. Various other biologically active peptides containing multiple prolyl groups have also been identified in digests, for example, of dietary proteins (mainly milk proteins), which led to the suggestion that these peptides that are released during digestion of dietary proteins in the gut may affect body functions by their opioid, immunomodulatory, or angiotensin-converting enzyme inhibitory activity. The extent to which and the speed with which a dietary protein is broken down to its constituent parts are therefore dependent on its composition (amino acid sequence) and on modifications that render it more resistant to hydrolysis. This also includes thermal effects of food processing that may cause the formation of Maillard products or that induce the conversion of free L-amino acids into their D-enantiomers. Studies with $^{15}$N-labeled dietary proteins in humans have demonstrated a quite variable extent of digestion and absorption as indicated by different ileal losses of amino acids depending on the nature of the protein administered.

Even intact proteins or large oligopeptides can be absorbed in small quantities in intact form either via the paracellular route or by microfold cells, but the bulk of protein is taken up in the form of di- and tripeptides and as free amino acids. For these end products of digestion, specialized carriers are found in the apical membrane of enterocytes.

 

## EPITHELIAL UPTAKE OF DI- AND TRIPEPTIDES

The multitude of intracellular peptidases with a strict specificity for the hydrolysis of di- and tripeptides suggested that such peptides may be absorbed in intact form followed by the intracellular release of free amino acids. The peptide transporter protein that carries di- and tripeptides into the cell was identified as a proton–peptide symporter that couples peptide uptake to the movement of protons down an electrochemical proton gradient. The PEPT1 protein contains 708 amino acids residues and 12 transmembrane domains with N- and C-terminal ends facing the cytosol. By coupling to proton flux, peptide transport occurs electrogenically regardless of the net charge of the substrate and causes intracellular acidification. The required proton gradient for peptide uptake is mainly, but not exclusively, provided by electroneutral proton/cation exchangers, such as the $Na^+/H^+$ antiporters that return protons to the lumen in exchange for $Na^+$ ions entering the cells. However, the main driving force for peptide transport is the negative membrane potential inside the cell. Normal dipeptides taken up into the cells are rapidly hydrolyzed by cytosolic peptidases and free amino acids are then delivered into the circulation. Although there is evidence for a basolateral efflux system for di- and tripeptides, the nature of this protein is not yet known.

Transport by PEPT1 shows a pronounced stereoselectivity, with peptides containing L-enantiomers of amino acid residues possessing higher affinity for transport than peptides containing D-enantiomers. Peptides consisting solely of D-amino acids do not show any relevant affinity for transport. One of the most striking features of PEPT1 is its capability of sequence-independent transport of all possible di- and tripeptides. This means that the 20 proteinogenic L-α-amino acids alone provide 400 different dipeptides and 8000 different tripeptides that can be transported by PEPT1. The ability of PEPT1 to also accept a variety of peptidomimetics, such as antibiotics of the aminocephalosporin and aminopenicillin classes, or selected angiotensin-converting enzyme inhibitors, such as captopril, explains the excellent oral availability of these drugs. The clinical importance of PEPT1 has been demonstrated in a variety of studies in different organisms including humans. Here, dipeptide mixtures have been shown to be superior to free amino acids for fast intestinal absorption and they are also more useful for enteral nutrition as they provide a lower osmolarity of the nutrition solution. Moreover, in a variety of gastrointestinal diseases, the peptide transporter has been found to be less affected by the pathophysiology than the amino acid transporters. Figure 1 displays the peptide transporter in the apical membrane of epithelial cells in the context of the various amino acid carriers that in concert allow efficient transcellular amino acid absorption.

## TRANSPORT OF FREE AMINO ACIDS ACROSS THE EPITHELIUM

When proteins and peptides undergo complete lumenal hydrolysis, free amino acids are released. The 20 proteinogenic amino acids and their derivatives resemble a heterogeneous group of compounds that differ in polarity, net charge, and molecular mass. It is therefore not surprising that membrane transporters with different substrate specificities are found. Whereas the carriers for neutral amino acids in most cases display a rather broad substrate specificity, other carrier types show much more specific interactions with a preference for either acidic or basic side chains of amino acids or for those with an aromatic structure. In addition, differences in the thermodynamic properties of the transport steps are observed with equilibrative systems and systems that are ion-dependent and show uphill transport capability. Almost all carriers display a pronounced stereoselectivity for transport of the physiologically important L-enantiomers of amino acids. Table I summarizes the main transport pathways for amino acids in mammalian cells subdivided into $Na^+$-dependent and $Na^+$-independent processes and the zrepresentative cDNAs that have been cloned and that express the corresponding transport activity in a target cell. Not surprisingly, there are numerous genetic and splice variants within the different transporter classes. However, at the structural level, most amino acid carriers show some common features with a peptide backbone of 350 to 700 amino acid residues that crosses the plasma membrane 10 to 12 times.

Enterocytes contain numerous amino acid transporters, some of which are found throughout the organism and others of which are specific for the apical or basolateral membranes of polarized cells. The transporters in the brush border membrane are primarily responsible for the absorption of amino acids from the intestinal lumen and those located on the basolateral surface of the enterocyte facilitate the transfer of amino acids between the enterocyte and the circulation. Influx across the basolateral membrane provides amino acids for the nutritional needs of the enterocyte in the absence of protein intake, whereas when proteins are digested and amino acids are absorbed, basolateral transporters

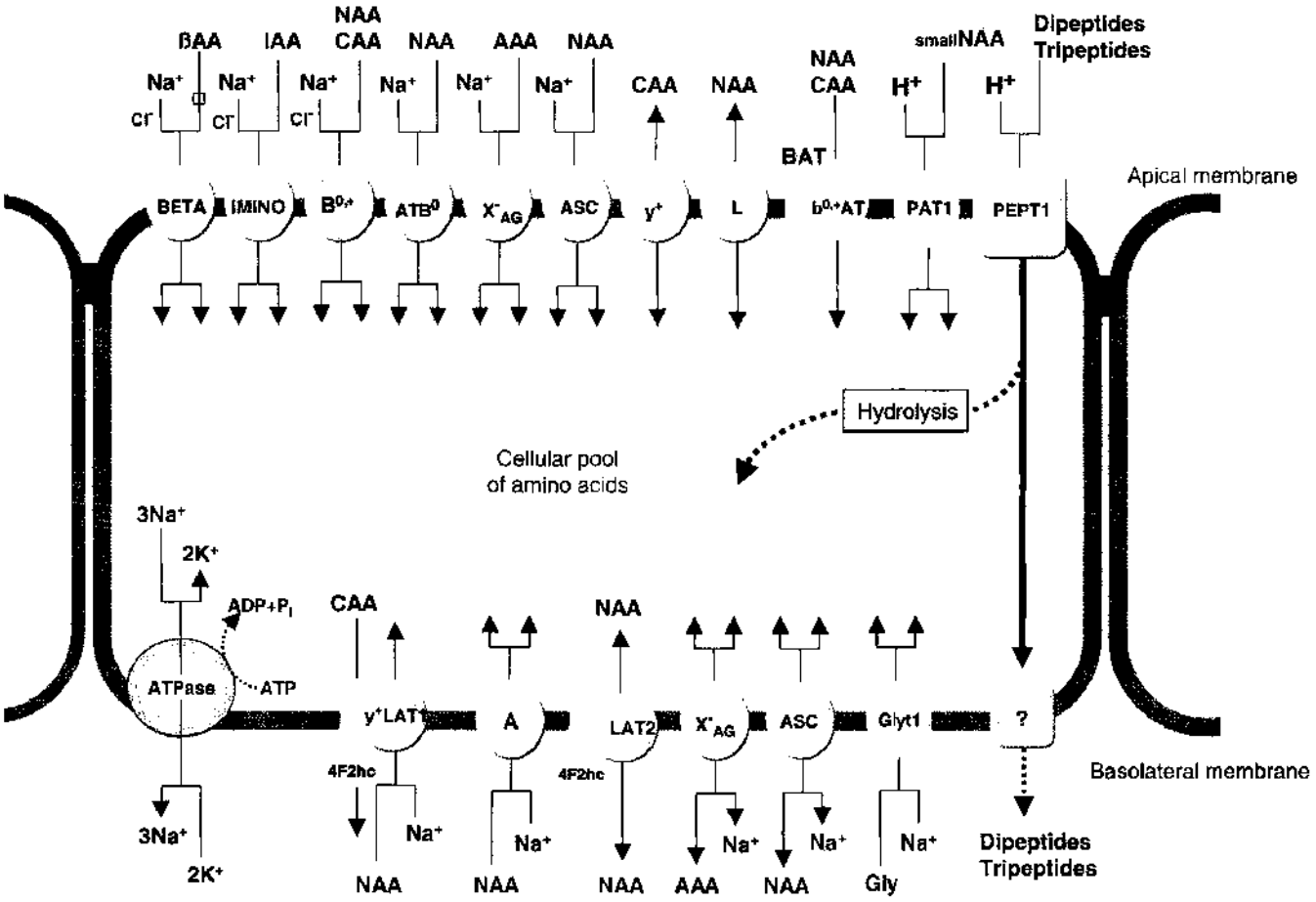


**FIGURE 1** Amino acid and peptide transporters in apical and basolateral membranes of intestinal epithelial cells responsible for transepithelial amino acid translocation. Dashed lines indicate the intracellular hydrolysis of di- and tripeptides by cytosolic peptidases. NAA, neutral amino acids; CAA, cationic amino acids; AAA, acidic amino acids; IAA, imino acids; βAA: β-amino acids; Gly, glycine.

mediate net amino acid efflux from the cell into the portal circulation. Figure 1 displays the various carriers in apical and basolateral membranes that are involved in transcellular amino acid transport.

The amino acid transporter class that is dependent on both $Na^+$ and $Cl^-$ gradients includes system IMINO, which transports imino acids such as proline, system BETA, a transporter of β-amino acids such as β-alanine, and system $B^{0,-}$ ($ATB^{0,-}$), which transports neutral, basic, and some D-enantiomeric amino acids. The second class contains the classical $Na^+$-dependent "secondarily active" transporters, including system $B^{0,+}$ and $ATB^0$, which transport a variety of neutral amino acids. Anionic amino acids are transported by system $X^-_{AG}$. System ASC has a preference for small neutral amino acids including alanine, serine, and cysteine. System A (mainly in basolateral membranes) transports neutral and methylated amino acids. The $Na^+$-independent transporters that operate in an "equilibrative" mode include system $y^+$ (the CAT proteins), which carries cationic amino acids, system $b^{0,+}$ ($ATb^{0,+}$), which transports cysteine as well as neutral and cationic amino acids, and system L (the LAT proteins), which recognizes mainly neutral amino acids. Members of the last group are particularly interesting in view of their molecular architecture. The novel structural characteristic of the LAT proteins is that they oligomerize via an extracellular disulfate bridge with a large second subunit to form a complex. In apical membranes, the glycoprotein heavy chain, designated BAT, associates with a LAT protein and the resulting complex possesses sodium-independent amino acid exchange capability. The other heavy chain, 4F2hc, can associate with various light chains (LAT proteins), with the complexes then mediating amino acid exchange across the basolateral membrane of epithelial cells as well as in nonpolarized cells. The heavy chains have a glycosidase-like extracellular domain attached to a single transmembrane

**TABLE 1 Amino Acid Transport Systems in the Plasma Membrane of Mammalian Cells**

| Transport system | Isolated cDNA(s) encoding this activity |
|---|---|
| $Na^+$ dependent | |
| A | ATA1-3 |
| N | SNI-3 |
| GLY | GlyT1-2 |
| ASC | ASC1-2 |
| BETA | GAT1-3, BGT-1 |
| IMINO | Not identified yet |
| $B^0$ | $ATB^0$ |
| $B^{0,-}$ | $ATB^{0,-}$ |
| $X^-_{AG}$ | EAAT1-5 |
| $Na^+$ independent | |
| L | 4F2hc/LAT(X) |
| $y^+$ | CAT1-3 |
| $b^{0,+}$ | BAT/$b^{0,+}$AT |
| $H^+$ dependent | |
| PAT | PAT1 (LYAAT-1), PAT2 |

domain, whereas the light chains vary in size but all possess 12 membrane-spanning domains, which are typical for polytopic membrane proteins with the amino- and carboxy-termini facing the cytosol. The carrier complexes can transport a wide range of neutral amino acids in an obligatory exchange mode, which means that they mediate the influx of certain amino acids in exchange for intracellular amino acids. The $b^{0,+}$ activity of the BAT-associated complex can in addition transport cationic amino acids in exchange for neutral amino acids, resulting in transport currents, whereas the $y^+$LAT1/4F2hc complex exchanges neutral amino acids in cotransport with sodium for intracellular cationic amino acids.

A new class of electrogenic proton-dependent amino acid symporters (PAT proteins) has been identified and cloned. From this class, the PAT1 carrier is expressed in the apical membrane of intestinal epithelial cells and mediates the cotransport of amino acids and derivatives that have a short side chain (glycine, alanine, serine, proline, γ-aminobutyric acid) by the coupling of substrate movement to proton movement down an electrochemical proton gradient. This transport activity consequently causes an intracellular acidification that requires apical sodium–proton exchangers for the control of intracellular pH, with proton export enhancing sodium uptake into epithelial cells.

The expression level of intestinal amino acid and peptide transporters can be adapted to dietary needs and a variety of hormones are involved in regulating protein expression and consequently the transport activity of the carriers that are responsible for the absorption of amino acids from dietary proteins.

## See Also the Following Articles

Digestion, Overview • Nutrient Transport, Regulation of

## Further Reading

Alpers, D. H. (1994). Digestion and absorption of carbohydrates and proteins. *In* "Physiology of the Gastrointestinal Tract" (L. R. Johnson, ed.). 3rd Ed., pp. 1723–1749. Raven Press, New York.

Chillaron, J., Roca, R., Valencia, A., Zorzano, A., and Palacin, M. (2001). Heteromeric amino acid transporters: Biochemistry, genetics, and physiology. *Am. J. Physiol. Renal Physiol.* **281**, F995–F1018.

Daniel, H. (1996). Function and molecular structure of brush border membrane peptide/$H^+$ symporters. *J. Membr. Biol.* **154**, 197–203.

Gaudichon, C., Bos, C., Morens, C., Petzke, K. J., Mariotti, F., Everwand, J., Benamouzig, R., Dare, S., Tome, D., and Metges, C. C. (2002). Ileal losses of nitrogen and amino acids in humans and their importance to the assessment of amino acid requirements. *Gastroenterology* **123**, 50–59.

Hausch, F., Shan, L., Santiago, N. A., Gray, G. M., and Khosla, C. (2002). Intestinal digestive resistance of immunodominant gliadin peptides. *Am. J. Physiol. Gastrointest. Liver Physiol.* **283**, G996–G1003.

Meisel, H., and Bockelmann, W. (1999). Bioactive peptides encrypted in milk proteins: Proteolytic activation and thropho-functional properties. *Antonie Van Leeuwenhoek* **76**, 207–215.

# Protein-Losing Disorders

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**enteropathy** Small intestinal disease.
**hypoalbuminemia** Abnormally low concentration of albumin in the blood.
**hypoproteinemia** Abnormally small amounts of total protein in the blood.
**intestinal absorption** Capacity of the intestinal mucosa to actively absorb digested food.
**intestinal permeability** Property of the intestinal mucosa to permit the passage (diffusion) of substances across the mucosa.
**malabsorption** Disorder of the process whereby digested food is actively incorporated or received by the gastrointestinal mucosa.
**maldigestion** Disorder of the process whereby ingested food is converted into material suitable for assimilation by the gastrointestinal mucosa.

**Extragastrointestinal causes of increased protein loss that need to be considered in the investigation of hypoproteinemia include trauma and sepsis. The processes leading to intestinal protein loss may be the result of defects in diet, metabolism, catabolism, absorption, or synthesis or may be related to specific gastrointestinal diseases. The goal of investigation and assessment of gastrointestinal protein loss, whether in the clinical or research setting, is to restore normal protein levels and to treat the underlying cause.**

## OVERVIEW OF ETIOLOGY

A number of factors can lead to hypoproteinemia and hypoalbuminemia, including dietary factors, maldigestion, malabsorption, reduced protein synthesis, increased catabolism, and protein loss via the gastrointestinal and renal systems or via other tissues in states of injury or inflammation.

### Normal Albumin Metabolism

Albumin is quantitatively the most important of the plasma proteins and is widely recognized as an indicator of general health status. The normal serum albumin concentration is usually between 35 and 50 g/liter, the mean being slightly higher in men than in women. Albumin is synthesized from prealbumin in the liver; in normal subjects, hepatic synthesis is equal to degradation, at approximately 1.5 g/day. The half-life of albumin is approximately 15 to 20 days. Increased concentration of albumin (>50 g/liter) is pathognomonic of dehydration. Hypoalbuminemia, however, may occur consequent with a number of factors.

### Malnutrition

On a global scale, malnutrition is the most common cause of hypoalbuminemia. Serum levels of prealbumin are exquisitely sensitive to changes in protein intake, reflecting its short half-life of approximately 2 days; however, as with albumin, prealbumin levels may change rapidly in the face of trauma or overwhelming sepsis even in the face of adequate nutritional intake. Albumin is not well suited for the purpose of assessing nutritional status because it may take weeks for levels to decline in response to malnutrition, reflecting its longer half-life in normal conditions; albumin levels may also drop dramatically in the face of acute illness due to increased losses and shifts in albumin distribution. Furthermore, low serum levels of albumin may take 3 or 4 weeks to return to normal, even in the setting of adequate nutrition in a recovering patient.

### Protein Maldigestion and Malabsorption

Maldigestion of proteins and malabsorption of amino acids are rare causes of hypoalbuminemia because of the reserve capacity of the functions involved in these processes. Protein digestion begins in the stomach with the action of gastric proteases, which are released as proenzymes that are activated by the low pH within the gastric lumen. Nevertheless, long-standing achlorhydria does not lead to hypoalbuminemia. Pancreatic enzymes, which likewise are secreted as inactive proenzymes, are activated by enterokinase within the microvilli of the brush border in the duodenum. Having been broken down into amino acids, dipeptides, and tripeptides, these are then absorbed by different classes of amino acid transporters on the brush border. Hypoalbuminemia is not, however, a preeminent

 

feature of severe pancreatic insufficiency and is only occasionally seen in celiac disease, in which there may also be substantial loss of albumin to the intestine.

### Reduced Synthesis

Albumin synthesis by the liver is dependent on changes in nutritional status, plasma oncotic pressure, cytokines, and hormones. In normal subjects, synthesis may be doubled in response to increased degradation or loss, but the synthesis of albumin may be considerably reduced in patients with severe chronic liver disease. The presence of ascites may significantly increase the total plasma volume and under these circumstances the total body albumin may be normal despite hypoalbuminemia.

### Increased Degradation

Hypoalbuminemia is common in seriously ill, injured, and septic patients. This appears not to be related directly to synthesis, which remains either unchanged or increased, but rather to shifts in the distribution into the extravascular space due to increased vascular permeability and changes in the catabolism of albumin in response to proinflammatory cytokines, generated in response to cardiac failure, infection, and other inflammatory stimuli.

## PROTEIN LOSS

Loss of protein via the kidney, gut, or other organs in combination with redistribution within extravascular tissues is the major cause of hypoproteinemia in the industrialized world. Such loss may occur in a number of settings.

### Renal

Nephrotic syndrome is characterized by proteinuria (greater than 3 g in 24 hours), peripheral edema, and hypoalbuminemia and is the most florid manifestation of renal protein loss. Heavy proteinuria with or without the other features of nephrotic syndrome may occur in a wide variety of renal and systemic disease. Approximately 30% of patients with hypoalbuminemia associated with renal disease have an underlying systemic disease such as diabetes, amyloidosis, or systemic lupus erythromatosis, although increased gastrointestinal loss is also often evident in these cases. The rest is due to primary renal disease in the form of minimal change nephropathy, focal glomerulosclerosis, and membranous nephropathy.

### Burns

Hypoalbuminemia is common in the intensive care unit setting, despite administration of albumin and aggressive nutritional support. In part, this relates to the extremely catabolic state of critically ill patients, but there is also a significant increase in leakage of albumin into the interstitial space consequent to endotoxemia and cytokine-induced changes in vascular permeability.

In the case of burns, thermal injury increases microvascular permeability, leading to increased loss of albumin into the extravascular space, into blisters, and as an exudate on the surface of burned skin; severe burns are almost invariably associated with infection leading to albumin displacement into the interstitial space, often resulting in the rapid development of hypoalbuminemia.

### Gastrointestinal

Gastrointestinal protein loss should be considered in patients when no other cause for hypoproteinemia can be identified. Whereas renal causes of protein loss are associated with predominant loss of albumin, gastrointestinal loss often leads to low levels of immunoglobulins (IgG, IgA, and IgM), clotting factors (fibrinogen), transferrin, and ceruloplasmin. Unlike liver disease, in which coagulopathy is common, the loss of clotting factors is rarely significant enough to be clinically evident. However, associated fat and carbohydrate malabsorption may lead to deficiency of fat-soluble vitamins. Numerous conditions affecting any part of the gastrointestinal tract can cause protein loss. The mechanisms by which protein loss occurs are as follows:

1. Mucosal injury, with or without inflammation, erosions, or ulcers, leading to a proteinaceous exudate.
2. Increased lymphatic pressure leading to loss of proteinaceous lymphatic fluid across the surface epithelium into the lumen.
3. Increased venous pressure (constrictive pericarditis, severe right heart failure, or portal hypertension) associated with transudation of protein.

Often a single disease may lead to hypoalbuminemia via a number of different mechanisms. Hypoalbuminemia occurs when the net protein loss from the gut exceeds the ability of the liver to synthesize such proteins.

#### *Mucosal Damage Associated with Inflammation, Erosions, or Ulcers*

Intestinal inflammation is a ubiquitous feature of most intestinal diseases. The reason for this is that what-

ever causes the initial damage, it results in impaired mucosal barrier function, i.e., increased intestinal permeability. The intestinal luminal contents, whether in the small or large bowel, are exceptionally toxic and proinflammatory. Any breach in the intestinal integrity is therefore associated with intestinal inflammation. If the inflammatory response is sufficiently robust, it will involve (as a passive bystander) the microcirculation with consequent leakage of albumin. In the vast majority of cases this increased loss of albumin is not clinically evident and can only be detected by direct measurement. Even when there is evidence of hypoalbuminemia, this is often not associated with any clinical signs or symptoms (serum albumin of 25–34 g/liter). However, when severe, the peripheral edema is uncomfortable and problematic if cardiac function is compromised. Common intestinal bacteria (*Salmonella*, *Shigella*, *Yersinia*, and *Campylobacter*) or viruses (measles and other enteroviruses and rotavirus) are all associated with significant intestinal inflammation, but clinically significant protein deficiency is rare unless food intake is severely compromised, such as is frequently the case in developing countries. Classical inflammatory bowel disease is the prototype of an inflammatory condition associated with erosions and ulcers. Despite the greater inflammatory intensity in ulcerative colitis, it is Crohn's disease that is more often associated with hypoalbuminemia, due to associated surgically induced malabsorption and decreased food intake. Intestinal protein loss in Crohn's disease correlates with clinical disease activity, suggesting inflammation is the driving force for the protein loss. Hypogammaglobulinemia and cellular immune deficiency may also cause protein loss and often have a presentation similar to that of Crohn's disease.

Gastrointestinal malignancy, carcinoma, lymphoma, Kaposi's sarcoma, and the systemic vasculitides can cause significant ulceration leading to marked protein loss. Nonsteroidal antiinflammatory drug (NSAID) enteropathy may lead to protein loss and hypoalbuminemia, either with or without the presence of ulceration. This is not an uncommon cause of hypoalbuminemia; about 10% of hospitalized patients with rheumatoid arthritis have problematic hypoalbuminemia due to NSAID-induced protein loss. It is of note that NSAID-induced enteropathy is clinically silent. Cytotoxic chemotherapy, via its effects on cell turnover, may cause loss of intestinal epithelial integrity, leading to increased exposure of the mucosal immune system to luminal antigens and thence to mucosal inflammation and protein loss.

A number of diseases affect the integrity of the mucosal cells and the intermediate cell junctions, without causing frank ulceration. These include celiac disease and tropical sprue. Here the protein loss follows disruption of the villous structure and the surface epithelium. Hypoalbuminemia is particularly common and severe in ulcerative jejunitis. A number of other conditions also result in protein loss across unulcerated mucosal surfaces, including allergic gastroenteritis and microscopic colitis.

Infiltration of the mucosa by amyloid protein in patients with amyloidosis can lead to significant protein loss via the gastrointestinal tract. These patients often have concurrent nephrotic syndrome due to renal disease, to which hypoalbuminemia is often attributed.

### *Gastropathies*

The development of giant gastric folds is associated with protein loss in the setting of a several gastric diseases. Menetrier's disease is widely recognized as being most commonly associated with significant protein loss. Hyperplasia of gastric crypts and superficial epithelium occurs in association with replacement of parietal cells with secretory glandular epithelium, leading to hypochlorhydria and increased gastric mucosal permeability.

Gastrointestinal infection has been reported to cause giant gastric folds. In children, cytomegalovirus infection has been associated with significant protein loss, but small intestinal involvement cannot always be ruled out. Infection with *Helicobacter pylori* has also been associated with the development of giant gastric folds and hypoalbuminemia, but this is an exceedingly rare complication. Eradication of *H. pylori* leads to complete resolution. Lymphocytic gastritis, also associated with *H. pylori*, may also present with a picture of giant mucosal folds, protein loss, and hypoalbuminemia.

### *Lymphatic Obstruction*

Obstruction of small bowel lymphatics, termed intestinal lymphangiectasia, leads to dilatation of the lymphatic channels and leakage of proteinaceous lymph fluid into the bowel lumen, resulting in hypoalbuminemia. Intestinal lymphangiectasia can be due to either a primary or a secondary disorder of the lymph vessels. Regardless of the cause, impaired drainage of lymph may result in reduced absorption of fat-soluble vitamins and chylomicrons.

### *Primary Lymphangiectasia*

Primary intestinal lymphangiectasia, a congenital maldevelopment of lymphatics, results in ectatic lymph vessels either focally or diffusely in the gut.

This condition is often associated with lymphoreticular abnormalities in other systems, including the skin. Within the gut, ectatic lymphatics may be found in any of the layers of the bowel wall containing such vessels (mucosa, submucosa, and subserosa).

The condition may be clinically silent or present with a combination of nausea, bloating, and episodic diarrhea. The diagnosis is based on the clinical, laboratory, and pathological findings. In severe cases, laboratory findings typically show reduced levels of albumin, immunoglobulins, clotting factors (although this is usually not clinically significant), and other plasma proteins. Barium follow-through may show thickened nodular mucosal folds, endoscopy characteristically shows a "snowflake" pattern overlying the small bowel mucosa, and histological examination shows dilated lymphatics, most prominently at the tip of the villi. Dilated lymph vessels can also be demonstrated on a lymphangiogram, using magnetic resonance imaging (MRI) or radionuclide imaging. Not uncommonly, the first suspicion of the disease comes from small bowel biopsy done because of malabsorption.

### *Secondary Lymphangiectasia*

Secondary lymphangiectasia may be associated with a wide variety of causes, reflecting either systemic or local disease, including cardiac failure, portal hypertension, infiltration of local and regional lymph nodes by primary or secondary malignancy, and reactive inflammatory changes associated with infection or inflammatory bowel disease.

## DIAGNOSIS OF PROTEIN-LOSING ENTEROPATHY

Diagnosis is usually based on the finding of hypoalbuminemia when there is no other cause for decreased protein production or increased loss from obvious sites. Gastrointestinal protein loss can be measured using radioisotopes ($^{51}$Cr-labeled albumin) or plasma clearance of $\alpha$1-antitrypsin. In clinical practice, these tests are not often performed because the diagnosis is evident from the setting of hypoalbuminemia in the context of a patient with gastrointestinal symptoms and concurrent histological and radiological findings consistent with the diagnosis. The tests, especially the $^{51}$Cr-labeled albumin technique, are, however, frequently used for research purposes to demonstrate therapeutic efficacy or to monitor disease.

## TREATMENT

Two principles, diagnostic intervention and nutritive therapy, underlie the treatment. Diagnostically, it is first appropriate to undertake correction of the underlying cause using any available therapy. It is important to ascertain whether the "intestinal inflammation" that leads to protein loss is in part driven by luminal bacteria and their degradation products. In the small bowel, which is predominantly populated by anaerobic bacteria, metronidazole is a logical treatment, in particular in those patients with NSAID enteropathy-induced hypoalbuminemia. If the protein loss is mainly from the colon, a cephalosporin may be beneficial. Second, it is important to maintain appropriate nutrition in order to enable patients to thrive.

### Nutrition

For patients with predominant lymph obstruction (lymphangiectasia), a diet that is low in saturated fat and high in protein should be encouraged. Medium-chain triglycerides can be used to supplement lipid intake. These fatty acids bypass the enteric lymphatics and enter the portal system directly. Medium-chain triglycerides have been shown to improve growth and reduce gastrointestinal symptoms in such patients. If the underlying cause for hypoproteinemia cannot be corrected, albumin infusion can be used for symptomatic and supportive treatment of hypoalbuminemia; however, albumin infusion should not be used as a means of nutritional supplementation.

Enteric protein supplementation using commercially available supplements can be used as required, but may not be necessary given sufficient intake of dietary protein in the form of meat and or other foodstuffs. When oral caloric and nutrient intake is insufficient to meet the needs of the patient, supplementary parenteral nutrition may be administered.

### See Also the Following Articles

**Lymph, Lymphatics, and Lymph Flow • Malabsorption • Malnutrition • NSAID-Induced Injury • Nutritional Assessment • Small Intestine, Absorption and Secretion**

### Further Reading

Alpers, D. H., Stenson, W. F., and Bier, D. M. (1995). "Manual of Nutritional Therapeutics," 3rd Ed. Little Brown, Boston.

Feldman, M. (1995). "Sleisenger & Fordtran's Gastrointestinal Disease," 5th Ed. W. B. Saunders, Philadelphia.

Heimberger, D. C., and Weinsier, R. L. (1997). "Handbook of Clinical Nutrition." Mosby, St. Louis.

# Protein-Losing Enteropathy, Pediatric

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**ascites** Excessive accumulation of fluid in the peritoneal cavity.
**enteropathy** Disease of the small intestine.
**hypoalbuminemia** An abnormally low concentration of albumin in the blood.

Protein-losing enteropathy in pediatric patients is a pathophysiologic process and not a specific disease. Treatment requires diagnosis of the underlying condition. In many instances, making the specific diagnosis and treating the condition totally resolve the process of protein-losing enteropathy; in other instances, they do not. The symptoms of protein-losing enteropathy may include vomiting, diarrhea, abdominal pain, and allergic symptoms and the signs include positional edema, facial and orbital swelling, ankle or leg edema, abdominal distension, and ascites. In patients with congenital or primary intestinal lymphangiectasia, asymmetric lymphedema may be a clue to an underlying disorder of the lymphatic channels. Patients with protein-losing enteropathy are typically hypoalbuminemic. Therefore, the initial steps in evaluation are to determine whether or not the infant or child is suffering from malnourishment, which could cause the hypoalbuminemia. Routine urinalysis should rule out proteinemia as a source of the hypoalbuminemia, and normal transaminases, bilirubin, and prothrombin time should exclude liver disease as the cause.

## DEMONSTRATION OF PROTEIN-LOSING ENTEROPATHY

Radiolabeled macromolecules, such as $^{131}$I-labeled polyvinylpyrrolidone and $^{51}$Cr-labeled albumin, were the tools originally used to detect protein-losing enteropathy (PLE) in adults and children. However, because of their hazards and inconvenience, mainly in the form of ionizing radiation, they are prohibited from being used in children. $^{99m}$Tc-labeled human serum albumin for scintigraphy has demonstrated that 0.5% of an intravenous dose normally appears in stool or urine within 24 h. Scintigraphic imaging has been used to demonstrate gastrointestinal protein loss.

Measurement of fecal α1-antitrypsin (Fα1AT) in random stool specimens has been shown to be an easily performed test for protein-losing enteropathy and is the test most widely used for infants, children, and adults. Fα1AT is independent of serum levels of α1-antitrypsin and fecal water content. It fulfills the criterion as a marker for protein-losing enteropathy and has several other advantages. It is a serum protein and is not found in the diet. Fecal levels demonstrate only protein levels entering the intestine from the intravascular space. Because its molecular weight of 50,000 Da is similar to that of albumin, Fα1AT should mimic the behavior of albumin. Because it is a protease inhibitor, it is excreted without degradation into the stool, and urine contamination of the stool will not invalidate the result. The greatest value of the study is that it can be performed on random specimens and is not affected by urine contamination.

Antitrypsin is excreted in two forms: alone and complexed with the enzyme. Levels of Fα1AT in stool are stable. Ninety-three percent of the Fα1AT remained after 72 h of incubation at 37°C, allowing transport prior to assay. Fα1AT is not found in gastric juice and is destroyed *in vitro* after 1 h of incubation at 37°C in gastric juice, but not in duodenal juice.

Because meconium contains higher levels of α1AT than does stool, this technique is not recommended in infants younger than 1 week of age.

This simple accurate test has broadened the number of disorders in which protein-losing enteropathy is found. Furthermore, its determination has made clinicians aware that a normal serum albumin does not preclude the presence of protein-losing enteropathy, since in one series 24% of patients with PLE had normal serum albumin levels.

Those patients with hypoalbuminemia and/or edema generally have 5 to 10 times the rate of protein excretion found in those with normal serum albumin levels and PLE.

Protein-losing enteropathy in infants and children can be divided into two broad categories: those conditions associated with mucosal erosion or ulceration and those conditions associated with lymphatic obstruction.

 

Disorders associated with mucosal erosion or ulceration may be further divided into those caused by infections and those arising from noninfectious causes.

## INFECTIOUS CAUSES OF PROTEIN-LOSING ENTEROPATHY

Gastrointestinal infections that typically are associated with mucosal erosions or ulceration or with damage to enterocytes or colonocytes display protein-losing enteropathy (see Table I).

Fα1AT is transiently increased in rotavirus diarrhea and its increase is related to the severity of diarrhea and its duration. Other viral infections, such as cytomegalovirus, can cause profound hypoalbuminemia and edema by injury to both small intestinal epithelium and colonic epithelium.

Parasites such as *Giardia lamblia* and *Strongyloides stercoralis* can also cause severe PLE. These infections can persist unless the diagnosis is made by examining stools for the parasite or its antigen and appropriate treatment is given to eradicate them.

*Clostridium difficile* and *Clostridium perfringens* can also cause PLE. Either identifying their toxins or growing the organisms will help to identify them as the cause.

Shigellosis, Salmonellosis, and *Campylobacter* infections all can cause PLE because they produce toxins that damage small intestinal and/or colonic mucosa. Although these infections may be self-limited, those patients with more severe infections are likely to display persistent signs and symptoms.

**TABLE I Pathologic Mechanisms and Their Manifestations for Protein-Losing Enteropathy in Infants and Children**

| |
|---|
| **Mucosal erosion or ulceration** |
| Infectious |
| *Clostridium difficile* |
| *Clostridium perfringens* |
| Cytomegalovirus |
| Rotavirus |
| Measles |
| *Giardia lamblia* |
| *Strongyloides stercoralis* |
| Salmonellosis |
| Shigellosis |
| *Campylobacteria* |
| *Escherichia coli* |
| Non infectious |
| Allergic gastroenteropathy |
| Eosinophilic gastroenteritis |
| Anastomotic ulcerations/ischemia |
| Atopic dermatitis |
| Burns |
| Gastroesophageal reflux |
| Gluten-sensitive enteropathy |
| Graft-versus-host disease |
| Henoch-Schoenlein purpura |
| Inflammatory bowel disease |
| Multiple polyposis |
| Necrotizing enterocolitis |
| Systemic lupus erythematosus |
| Lymphatic obstruction |
| Intestinal lymphangiectasia |
| Arsenic poisoning |
| Familial |
| Heart disease |
| Nephrotic syndrome |
| Noonan's syndrome |
| Primary |
| Cirrhosis with portal hypertension |
| IVC thrombosis post-OLT |

## NONINFECTIOUS INFLAMMATORY DISORDERS THAT CAUSE PROTEIN-LOSING ENTEROPATHY

Allergic gastroenteropathy or eosinophilic gastroenteritis is an entity that typically presents after the first 6 months of life. Although most cases manifest during infancy, it can develop at almost any age. These patients are typically characterized as having hypoalbuminemia, peripheral eosinophilia, the presence of Charcot-Leyden crystals in stool, iron deficiency anemia, and elevated immunoglobulin E levels. They may have associated asthma, eczema, and allergic rhinitis. Gastrointestinal symptoms may include vomiting, diarrhea, and abdominal pain.

In infants, milk protein may be the predominant protein that causes the injury. However, in some individuals, multiple proteins may be responsible for the condition and dietary restriction may be very difficult to accomplish. Usually, if the protein responsible for the allergy is removed from the diet, the injury is reversed and the markers of injury return to normal values. Corticosteroids can be used to block the injury and reverse the protein-losing enteropathy but corticosteroid use is not a good long-term solution.

Anastomotic ulcers following distal small bowel resection cause recurrent iron deficiency and PLE with or without hypoalbuminemia.

Twenty-five percent of patients undergoing bone marrow transplantation develop graft-versus-host disease involving the intestine. It is typically associated with a severe watery diarrhea. One must make certain that there are no associated infections, such as

cytomegalovirus enterocolitis, in this type of patient; this infection is curable with ganciclovir.

Inflammatory bowel disease is an important cause of protein-losing enteropathy. The severity of hypoalbuminemia and the degree of protein loss are greater in patients with Crohn's disease than in those with ulcerative colitis and greater in those with diffuse small bowel disease than in those with limited small bowel or colonic disease.

At least half of all patients with Crohn's disease have hypoalbuminemia. Many more patients with normal serum albumin levels also have protein-losing enteropathy.

Celiac disease or gluten-sensitive enteropathy is also associated with protein-losing enteropathy because of the damage to the villous structure of the small intestine. It may be mild or severe depending on the extent of the damage to the small intestine and the length of time the damage has persisted. It is reversible with adherence to a strict gluten-free diet. Within 14 days of the patient initiating the diet, the protein-losing enteropathy may be reversed.

Necrotizing enterocolitis may be associated with PLE because of the damage to the small intestine and colon caused by the disease process.

Multiple juvenile polyposis syndrome with chronic blood loss and protein-losing enteropathy has been described. These children typically present in infancy. They have a poor prognosis because of the hundreds of polyps occurring throughout the colon, small intestine, and stomach.

It is unclear why burn victims have increased F$\alpha$1AT levels. The level of elevation even in severely burned children is not great. The clinical importance is unclear.

There are a variety of other conditions rarely associated with PLE but in all of these conditions the characteristic feature is the presence of an inflammatory process.

## LYMPHATIC OBSTRUCTION

Intestinal lymphangiectasia describes a group of conditions in which dilation of the lacteals, the fine, thin-walled lymphatic channels extending up into the small bowel villi, results from obstruction of the flow of lymph through the thoracic duct and into the superior vena cava. Fat intake leads to further distension and rupture of the lacteals, resulting in steatorrhea and drainage of lymph into the intestine. The resulting loss of protein, lymphocytes, and immunoglobulins ultimately leads to hypoalbuminemia, lymphopenia, and hypogammaglobulinemia.

Intestinal lymphangiectasia may be primary or secondary to other causes of lymphatic obstruction (see Table II). A variety of familial forms with intestinal lymphangiectasia have been described. Some have been described with asymmetrical lymphedema in addition to intestinal lymphangiectasia.

The hypoalbuminemia and lymphopenia may be reversed if the patient responds to dietary therapy. Patients with lymphangiectasia may have an increased risk of infection when untreated secondary to the loss of gammaglobulin and immunocytes. Other patients with Noonan's syndrome have been described with multifocal lymphatic dysplasia. Some but not all of these patients respond to a diet low in long-chain triglycerides (LCT) that provides less than 10% of the lipid as LCT and receives it as medium-chain triglycerides. However, in rare cases, dietary restrictions of fat even below that level did not help reverse the hypoalbuminemia and lymphopenia. A rare case of arsenic poisoning has also been associated with PLE.

**TABLE II Intestinal Lymphangiectasia—Disorders Associated with Enteric Protein Loss, Lymphopenia, and Hypoalbuminemia**

| |
|---|
| Primary intestinal lymphangiectasia |
| Isolated |
| Associated with lymphatic abnormalities elsewhere in the body |
| Secondary intestinal lymphangiectasia |
| Cardiovascular anomalies |
| Congestive heart failure |
| Constrictive pericarditis |
| Budd–Chiari syndrome |
| Glenn shunt |
| Fontan procedure |
| Superior vena cava thrombosis |
| Inferior vena cava thrombosis |
| Mesenteric lymphatic involvement |
| Lymphomas |
| Tuberculosis |
| Sarcoidosis |
| Radiation therapy |
| Volvulus |
| Intestinal inflammatory diseases |
| Systemic lupus erythematosus |
| Tuberculosis |
| Behçet's syndrome |
| Crohn's disease |
| Drugs |
| Arsenic |
| Chemotherapeutic agents |
| Thoracic duct obliteration |
| Iatrogenic |
| Mediastinal tumor |

Cardiac disorders or surgical procedures resulting in transmission of elevated pressure from the right atrium into the superior vena cava and thoracic duct, including clinically silent constrictive pericarditis, have been associated with the development of intestinal lymphangiectasia.

Early survival after the Fontan operation for a single ventricle has improved substantially since its inception; however, late-term complications continue to be problematic. One such complication of PLE is seen in 3 to 15% of patients with Fontan procedures. Recently some investigators have shown that increased mesenteric vascular resistance is characteristic of those with Fontan's and PLE.

Recent studies have shown that portal hypertension in some patients with chronic liver disease may result in PLE. The elevated portal pressure may lead to secondary intestinal lymphangiectasia. Reversal of this phenomenon has been observed after liver transplantation.

Obstruction to hepatic venous outflow as occurs in Budd-Chiari syndrome can also cause PLE as can inferior vena cava occlusion following orthotopic liver transplantation.

Children with the rare condition of hypertrophic gastropathy or Menetrier's disease (also known as transient hypertrophic gastropathy) present with abdominal pain and vomiting. They gradually develop edema and ascites. The cause of some of these cases has been suggested to be allergy and other cases appear to be caused by cytomegalovirus infection. Cases of transient hypertrophic gastropathy have been described in children with *Helicobacter pylori* infections.

## See Also the Following Articles

**Celiac Disease, Pediatric • Colitis, Ulcerative (Pediatric) • Cow Milk Protein Allergy • Crohn's Disease, Pediatric • Gastroesophageal Reflux Disease (GERD) and Congenital Esophageal Obstructive Lesions, Pediatric • Lymph, Lymphatics, and Lymph Flow • Parasitic Diseases, Overview**

## Further Reading


Catassi, C., Cardinali, E., D'Angelo, G., *et al.* (1986). Reliability of random fecal α-antitrypsin determination on nondried stools. *J. Pediatr.* 109, 500–502.

Chang, J. M., Hwang, S. J., Chen, H. C., and Lai, Y. H. (2002). Edema due to protein-losing enteropathy—A disorder rarely considered by nephrologists. *Clin. Nephrol.* 57, 392–397.

Chaubal, N., Shah, M., Dighe, M., Ketkar, D., and Joshi, A. (2002). Juvenile polyposis of the colon: Sonographic diagnosis. *J. Ultrasound Med.* 21, 1311–1314.

Cheung, Y. F., Tsang, H. Y., and Kwok, J. S. (2002). Immunologic profile of patients with protein-losing enteropathy complicating congenital heart disease. *Pediatr. Cardiol.* 23, 587–593.

Cohen, H. A., Shapiro, R. P., Frydman, M., *et al.* (1991). Childhood protein losing enteropathy associated with *Helicobacter pylori* infection. *J. Pediatr. Gastroenterol. Nutr.* 13, 201–203.

Hamada, A., Kondoh, T., Kamei, T., Tominaga, N., Tsuru, A., Matsumoto, T., Matsuzaka, T., and Moriuchi, H. (2002). Protein-losing enteropathy complicated with recurrent convulsions and developmental delay in a 4-month-old boy. *Pediatr. Int.* 44, 686–689.

Harms, H. K., Zimmer, K. P., Kurnik, K., Bertele-Harms, R. M., Weidinger, S., and Reiter, K. (2002). Oral mannose therapy persistently corrects the severe clinical symptoms and biochemical abnormalities of phosphomannose isomerase deficiency. *Acta Pediatr.* 91, 1065–1072.

Holzknecht, N., Helmberger, T., Beuers, U., Rust, C., Wiebecke, B., and Reiser, M. (2002). Cross-sectional imaging findings in congenital intestinal lymphangiectasia. *J. Comput. Assist. Tomogr.* 26, 526–528.

Lee, W. S., John, P., McKiernan, P., de Goyet, J. D. V., and Kelly, D. A. (2002). Inferior vena cava occlusion and protein-losing enteropathy after liver transplantation in children. *J. Pediatr. Gastroenterol. Nutr.* 34, 413–416.

Marino, B. S. (2002). Outcomes after the Fontan procedure. *Curr. Opin. Pediatr.* 14, 620–626.

Rychik, J., and Gui-Yang, S. (2002). Relation of mesenteric vascular resistance after Fontan operation and protein-losing enteropathy. *Am. J. Cardiol.* 90, 672–674.

Rychik, J., and Spray, T. L. (2002). Strategies to treat protein-losing enteropathy. *Semin. Thorac. Cardiovasc. Surg. Pediatr. Card. Surg. Annu.* 5, 3–11.

Seok, J. W., Kim, S. J., Lee, S. H., Kim, I. J., and Kim, Y. K. (2002). Protein-losing enteropathy detected on Tc-99m HAS and TC-99m MDP scintigraphy. *Clin. Nucl. Med.* 27, 431–433.

Silverman, A., and Roy, C. C. (1983). "Pediatric Clinical Gastroenterology," 3rd Ed., p. 377. Mosby, St. Louis, MO.

Tokatli, A., and Ozsoylu, S. (1991). Ménétrier disease in a child. *J. Pediatr. Gastroenterol. Nutr.* 12, 404–406.

# Proton Pump Inhibitors

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**gastric $H^+,K^+$-ATPase** A $P_2$-type ion-motive ATPase enzyme that carries out an electroneutral exchange of cytoplasmic protons for extracytoplasmic potassium.

**omeprazole** The prototypical, clinically used proton pump inhibitor.

**proton pump inhibitor** An inhibitor of gastric $H^+,K^+$-ATPase activity.

**Proton pump inhibitors make up a class of compounds that inhibit gastric $H^+,K^+$-ATPase activity and thereby inhibit gastric acid secretion. Controlling acid secretion is important in healing gastric ulcer, peptic ulcer, and related diseases. Gastric acid is secreted from the parietal cell on stimulation by histamine, acetylcholine, and gastrin. These stimulants change the morphology of the parietal cell from the resting state to the stimulated state with relocation of the gastric $H^+,K^+$-ATPase from the tubular vesicles to the apical canalicular membranes. The gastric $H^+,K^+$-ATPase transports $H^+$ ($H_3O^+$) ion from the cytoplasmic region to the lumen with the exchange of $K^+$ from the lumen to the cytoplasmic side. The gastric $H^+,K^+$-ATPase consists of two subunits: one is the α-subunit, composed of approximately 1034 amino acids, and the other is the β-subunit, which has approximately 290 amino acids and six or seven N-linked glycosylation sites depending on species. The $H^+,K^+$-ATPase α-subunit has 10 transmembrane segments and the β-subunit has 1 transmembrane segment. Inhibition of this acid pump enzyme is known to be the most effective therapy for controlling gastric acid secretion.**

## INTRODUCTION

The proton pump inhibitors (PPIs) can be classified into two groups: irreversible and reversible inhibitors. Irreversible covalent inhibitors are either substituted 2-(pyridinemethylsulfinyl)benzimidazoles or a similar structure, pyridylmethylsulfinyl pyrido-imidazole, which inhibit the pump enzyme by covalently binding to the α-subunit of the $H^+,K^+$-ATPase. Reversible proton pump inhibitors are mostly $K^+$-competitive inhibitors, which inhibit the gastric $H^+,K^+$-ATPase activity by competing with potassium ions.

Since a substituted benzimidazole was first reported to inhibit the $H^+,K^+$-ATPase, many PPIs have been synthesized and are now in clinical use. Typical proton pump inhibitors in clinical use are listed in Fig. 1.

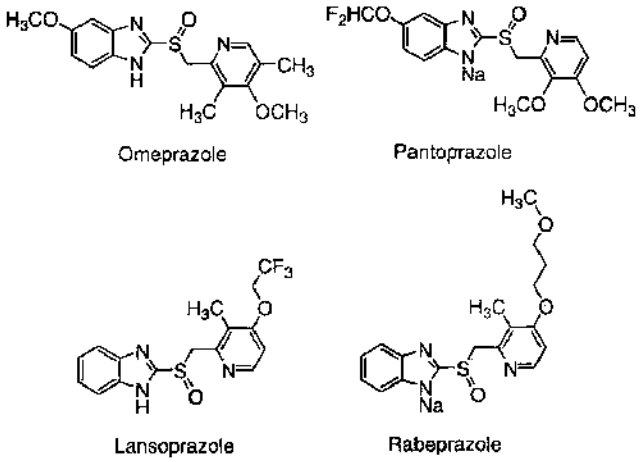
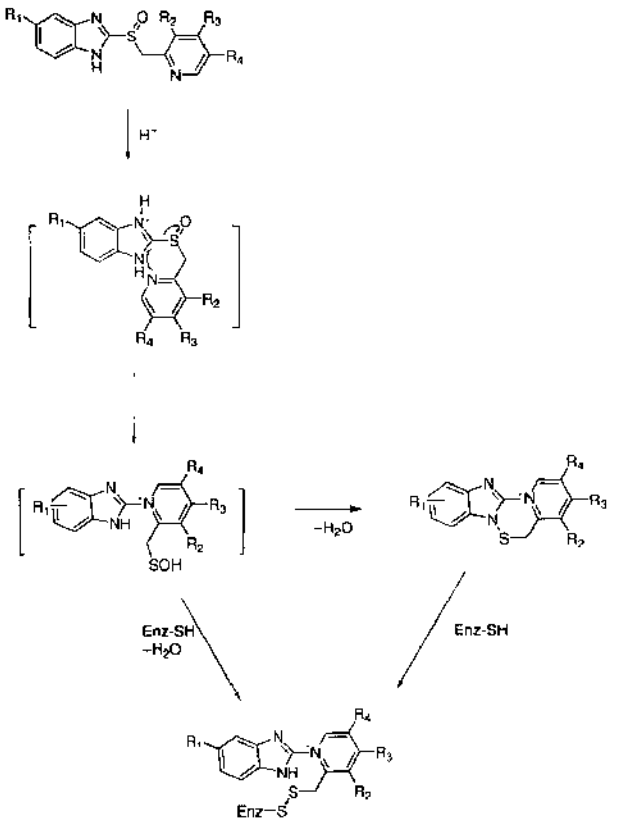



FIGURE 1 Chemical structure of irreversible proton pump inhibitors in clinical use.

## IRREVERSIBLE COVALENT BINDING INHIBITORS

Timoprazole was the first compound that was found to inhibit the gastric $H^+,K^+$-ATPase by covalent binding. This compound is 2-(pyridylmethyl)sulfinylbenzimidazole. The first pump inhibitor used clinically was omeprazole (2-[[3,5-dimethyl-4-methoxypyridin-2-yl]methylsulfinyl]-5-methoxy-1H-benzimidazole). Compounds in this class are acid-activated prodrugs. For example, omeprazole, due to being a weak base, accumulates in the acidic space of the parietal cell and, by acid-catalyzed rearrangement, becomes a thiol-reactive cationic sulfenic acid and/or sulfenamide that binds to cysteinyl-SH groups to form disulfides as shown in Fig. 2. The activation is initiated by the protonation of the pyridine nitrogen, which is followed by transfer of this proton to the benzimidazole nitrogen, which then increases the electrophilic reactivity of the C-2 of the benzimidazole. Now pyridine is ready to attack this 2-position carbon of benzimidazole to form sulfenic acid, which then rearranges to form




| | $R_1$ | $R_2$ | $R_3$ | $R_4$ |
|---|---|---|---|---|
| Omeprazole | $-OCH_3$ | $-CH_3$ | $-OCH_3$ | $-CH_3$ |
| Pantoprazole | $-OCHF_2$ | $-OCH_3$ | $-OCH_3$ | $-H$ |
| Lansoprazole | $-H$ | $-CH_3$ | $-OCH_2CF_3$ | $-H$ |
| Rabeprazole | $-H$ | $-CH_3$ | $-OCH_2CH_2CH_2OCH_3$ | $-H$ |

**FIGURE 2** Mechanism of action of irreversible proton pump inhibitors. Proton pump inhibitor, a substituted benzimidazole compound, accumulates in the acidic lumen and is converted to active sulfenic acid and (or) sulfenamide, which bind(s) extracytoplasmic cysteines of the gastric $H^+,K^+$-ATPase.

sulfenamide. The three other proton pump inhibitors, lansoprazole, pantoprazole, and rabeprazole, also undergo similar acid-catalyzed rearrangement to form active sulfenic acids and/or sulfenamides. Although all of the proton pump inhibitors accumulate in the secretory canaliculus of the stimulated parietal cell by virtue of being protonatable weak bases, they show variation in the rate of acid activation. The rate of acid activation is fastest for rabeprazole, equal for omeprazole and lansoprazole, and slowest for pantoprazole. Also, substituted benzimidazole inhibitors showed slightly different effects depending on the inhibitor structure. For instance, omeprazole-bound enzyme is favored in the $E_2$ form. Another inhibitor, rabeprazole (E3810), 2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]methylsulfinyl]-1H-benzimidazole, stabilized the $E_1$ form of the enzyme after binding. It is claimed that the $K^+$-dependent dephosphorylation from the phosphoenzyme was inhibited in the rabeprazole-bound enzyme but not in the omeprazole-bound enzyme, whereas phosphoenzyme formation in the absence of $K^+$ was inhibited in both the E3810- and the omeprazole-bound enzymes.

Omeprazole binds to cysteines in the extracytoplasmic regions of M5/M6 (Cys-813) and M7/M8 (Cys-892). Pantoprazole binds only to the cysteines in M5/M6, Cys-813 and Cys-822, and lansoprazole binds to Cys-321 in M3/M4, to Cys-813 in M5/M6, and to Cys-892 in M7/M8. These data suggest that, of the 28 cysteines in the $\alpha$ subunit, only the cysteines present in the M5/M6 domain are important for inhibition of acid secretion by the PPIs.

Interestingly, the half-time of recovery of acid secretion in rats following omeprazole treatment was measured to be ~15 h, whereas pump protein half-life is 54 h. If omeprazole binding to the gastric $H^+,K^+$-ATPase is irreversible, recovery of acid secretion after omeprazole inhibition should be similar to *de novo* synthesis of pump protein, i.e., approximately 54 h. The shorter half-life of acid secretion recovery compared to the half-life of pump enzyme suggests that there must be disulfide cleavage between the pump enzyme and the bound omeprazole moiety and reactivation of inhibited pump. In humans, the half-life of the inhibitory effect on acid secretion is ~28 h for omeprazole and ~46 h for pantoprazole. Only pantoprazole showed a half-life of a duration similar to that of a protein half-life. It was shown that recovery of acid secretion following inhibition by all PPIs other than pantoprazole may depend on both protein turnover and reversal of the inhibitory disulfide bond. In contrast, recovery of acid secretion after pantoprazole may depend entirely on new protein synthesis.

Another type of irreversible proton pump inhibitor is the pyridinylmethylsulfinyl imidazopyridines, such as TU-199 and anilinomethylsulfinyl benzimidazole. Neither is yet available for clinical use.

## $K^+$-COMPETITIVE INHIBITORS

$K^+$-competitive inhibitors can be thought of as acid pump antagonists. These antagonists contain protonatable nitrogens but have a variety of core structures. One type is represented by the imidazopyridine derivatives such as SCH28080; others are piperidinopyridines, substituted 4-phenylaminoquinolines, pyrrolo[3,2-c]quinolines, guanidino-thiazoles, 2,4-diaminopyrimidine derivatives, and scopadulcic acid.

SCH28080, a substituted imidazo[1,2α] pyridine, is the best defined compound among other reversible proton pump inhibitors. SCH 28080, 3-cyanomethyl-2-methyl-8-(phenylmethoxy) imidazo[1,2α]pyridine, inhibited the $H^+,K^+$-ATPase competitively with $K^+$. It binds to free enzyme extracytoplasmically in the absence of substrate to form $E_2$(SCH 28080) complexes. SCH 28080 occupies the same space in the lumen where omeprazole binds. SCH28080 inhibits ATPase activity with high affinity in the absence of $K^+$. SCH 28080 has no effect on spontaneous dephosphorylation but inhibits $K^+$-stimulated dephosphorylation, presumably by forming a $E_2$-P · [I] complex. Hence, SCH 28080 inhibits $K^+$-stimulated ATPase activity by competing with $K^+$ for binding $E_2P$. Steady state phosphorylation is also reduced by SCH 28080, showing that this compound also binds to the free enzyme. At present, no acid pump antagonist is available for clinical use but some are in development.

## CLINICAL USE

Proton pump inhibitors are orally active and used for the therapy of gastric ulcer, duodenal ulcer, gastroesophageal reflux disease, Zollinger-Ellison syndrome, and, combined with antibiotics, for eradication of *Helicobacter pylori*. The primary effect of these proton pump inhibitors is gastric acid suppression. The degree of acid suppression correlates with healing rates for reflux esophagitis and peptic ulcer. Rabeprazole is fast-acting with pain relief. Pantoprazole shows a longer half-time of restoration of acid secretion. Omeprazole and pantoprazole show an increase in acid inhibitory effect over several days of repeated administration. Lansoprazole shows maximal inhibition after the first day. There is poor correlation between maximal plasma drug concentration ($C_{max}$) and the degree of acid suppression. Instead, the area under the plasma concentration–time curve (AUC) correlates with acid suppression. Among proton pump inhibitors, omeprazole 20 mg and rabeprazole 20 mg showed a significantly lower AUC than pantoprazole 20 and 40 mg and lansoprazole 30 mg. However, all proton pump inhibitors used clinically, omeprazole, lansoprazole, pantoprazole, and rabeprazole, show approximately equivalent potency for gastric acid suppression. Pantoprazole is available for intravenous use and is used to suppress acid secretion in intensive care situations.

All proton pump inhibitors are extensively metabolized in liver by P450 cytochromes. People with hepatic impairment have shown a 7- to 9-fold increase in the AUC with a prolongation of the plasma half-life to 4–8 h. Approximately 3% of the population with a genetic polymorphism are poor metabolizers and show a 5- to 10-fold increase of AUC. Elderly people showed a 50–100% increase in the AUC since hepatic metabolism was poor. All four proton pump inhibitors are metabolized mainly by CYP 2C19 and CYP 3A4. CYP 2C19 generates hydroxylation of proton pump inhibitor, which is responsible for 80% of clearance in the case of omeprazole. CYP 3A4 generates sulfonylation of proton pump inhibitors.

Recently, S-omeprazole became available for clinical use. Omeprazole is a racemate consisting of S- and R- enantiomers. The R-form of omeprazole is sensitive to CYP 2C19 and CYP 3A4 enzymes and the S-form is less sensitive to these CYP enzymes. S-omeprazole has a longer plasma half-life than omeprazole, providing longer acid suppression.

Acid suppression correlates with healing rates for reflux esophagitis and peptic ulcer. Good healing for reflux esophagitis was achieved when the intragastric pH was greater than 4 for 16 h/day and healing for peptic ulcer was best achieved when the intragastric pH was greater than 3. In patients with reflux esophagitis, lansoprazole 30 mg provided faster symptom relief than omeprazole 20 mg; however, no significant difference was observed compared to omeprazole 40 mg in terms of healing rates and symptom relief. Rabeprazole 20 mg and pantoprazole 40 mg provided equivalent healing rates and symptom relief compared to omeprazole 20 mg. In peptic ulcer disease and duodenal ulcers, all four proton pump inhibitors showed very similar efficacy, whereas rabeprazole and lansoprazole claimed a little fast symptom relief.

*H. pylori* has been successfully eradicated by triple-therapy regimens: clarithromycin, amoxycillin, and proton pump inhibitor. There are no significant differences among four proton pump inhibitors, omeprazole, lansoprazole, pantoprazole, and rabeprazole, when used for this purpose.

## See Also the Following Articles

**Duodenal Ulcer • Gastric Acid Secretion • Gastric $H^+,K^+$-ATPase • Gastric Ulcer • Gastrinoma • Gastroesophageal Reflux Disease (GERD) • *Helicobacter pylori* • Pharmacology, Overview**

## Further Reading

Abelo, A., Andersson, T. B., Antonsson, M., Naudot, A. K., Skanberg, I., and Weidolf, L. (2000). Stereoselective metabolism of omeprazole by human cytochrome P450 enzymes. *Drug Metab. Dispos.* 28, 966–972.

Sachs, G., Briving, C., Shin, J. M., Hersey, S., and Wallmark, B. (1995). The pharmacology of the gastric acid pump, the $H^+,K^+$-ATPase. *Annu. Rev. Pharmacol. Toxicol.* 35, 277–305.

Shin, J. M., Bayle, D., Bamberg, K., and Sachs, G. (1998). The gastric $H^+,K^+$-ATPase. *In* "Advances in Molecular and Cell Biology," Vol. 23A, pp. 101–142. JAI Press, Greenwich, CT.

Shin, J. M., and Sachs, G. (2002). Mechanism of restoration of acid secretion following treatment with proton pump inhibitors. *Gastroenterology* 123(5), 1588–1597.

Stedman, C. A. M., and Barclay, M. L. (2000). Review article: Comparison of the pharmacokinetics, acid suppression and efficacy of proton pump inhibitors. *Aliment. Pharmacol. Ther.* 14, 963–978.

# Pruritus of Cholestasis

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**nociceptive** Unpleasant or painful sensation.

**central opioidergic neurotransmission** Signals in the central nervous system carried out by opioid peptides and receptors.

**opioids** Endogenous peptides with an affinity for opioid receptors.

**Pruritus is a complication of liver disease, in particular when associated with cholestasis. Its etiology is unknown; most treatments have been empirical and unsatisfactory. Intractable pruritus is an indication for liver transplantation. The pruritus of cholestasis does not correlate with serum markers of liver disease.**

## ETIOLOGY OF THE PRURITUS OF CHOLESTASIS

It is inferred that the substance(s) that mediates pruritus in cholestasis is made in the liver and excreted in bile. In support of this inference is the finding that patients with cholestasis report disappearance of pruritus after liver transplantation and after removal of blockage in cases of extrahepatic biliary obstruction.

### Bile Acids

Bile acids accumulate in the plasma of patients with cholestasis; however, there is no scientific evidence that demonstrates their role in the mediation of the pruritus of cholestasis.

In the context of bile acids as pruritogens in cholestasis, three observations must be considered: (1) the accumulation of bile acids in the skin or interstitial fluid may not have any relevance to the pruritus (2) there are patients with cholestasis and high serum concentrations of bile acids who do not report pruritis, and (3) spontaneous relief of pruritus does not correlate with decreases in serum bile acids.

### Histamine

Histamine is pruritogenic. Histamine-mediated lesions, such as skin erythema and edema, however, are not skin findings in patients who experience pruritus secondary to cholestasis. The lack of specific antipruritic effect of antihistamines in patients with the pruritus of cholestasis does not support a role of histamine in this type of pruritus.

### The Endogenous Opioid System

Three lines of evidence suggest that patients with cholestasis have alterations in the endogenous opioid system: (1) an opioid withdrawal-like reaction can be experienced by patients with cholestasis after the administration of opiate antagonists, (2) the concentration of opioid peptides in the serum of patients with cholestasis is higher than that of control subjects, and (3) the immunoreactivity of Met-enkephalin, one of the endogenous opioid peptides, is enhanced in the liver of patients with primary biliary cirrhosis, a liver disease associated with cholestasis, in contrast to that of the disease control livers. The opiate withdrawal-like reaction suggests that in cholestasis there is increased central opioidergic neurotransmission.

**TABLE I Therapies for the Pruritus of Cholestasis**

| Drug | Rationale for use in the treatment pruritus of cholestasis | Dose | Potential side effects |
|---|---|---|---|
| Cholestyramine | Decrease in enterohepatic circulation of bile acids | 4 g pre- and postbreakfast and after other meals, not to exceed 16 g per day | Bloating, constipation, malabsorption |
| Antihistamines | Unknown | Variable | Sedation, dry mouth |
| Phenobarbital | Enhancement of pruritogen excretion | Variable | Sedation |
| Rifampicin | Unknown | 300 to 450 mg po per day in divided doses | Hepatotoxicity |
| Opiate antagonists (naloxone, naltrexone) | Antagonism of endogenous opioids | Naloxone: 0.4 mg iv bolus followed by infusions of 0.2 μg/kg/min Naltrexone: 50 mg/day | Opiate withdrawal-like reaction, hepatotoxicity |
| Serotonin type 3 receptor antagonist (ondansetron) | Interference with mechanisms of nociception | 4 to 8 mg po per day | Constipation, headache |

Drugs with agonist properties at opioid receptors are pruritogenic, in particular, when centrally administered. Opiate-induced pruritus is effectively treated with opiate antagonists. The pruritogenic property of opiate drugs, the suggestion of increased opioidergic tone in cholestasis, and the anecdotes reporting that opiate antagonists decreased the pruritus of cholestasis suggest that endogenous opioids mediate this type of pruritus, at least in part. A central mechanism has been proposed. Various clinical trials of opiate antagonists for the treatment of the pruritus of cholestasis were conducted. These studies included objective methodology, which allowed for the recording of scratching activity, the behavior that specifically results from pruritus, independent of gross body movements. Opiate antagonists were associated with a decrease in the perception of pruritus and scratching activity. These results support a role of endogenous opioids in the pruritus of cholestasis.

### Serotonin System

The serotonin system is involved in the mediation of nociceptive stimuli. Ondansetron, an antagonist of type 3 serotonin receptors, which are found both in the central nervous system and on peripheral nerves, was reported to decrease the pruritus of cholestasis in studies that used subjective methodology.

## TREATMENT OF THE PRURITUS OF CHOLESTASIS

### Drugs

Table I lists some of the drugs used to treat the pruritus of cholestasis. Some drugs appear to have a rationale for their use and some do not. The doses listed are summarized from published studies; they should be individualized. For a complete review of side effects, the reader is referred to original sources.

### Invasive Procedures to Treat the Pruritus of Cholestasis

The need to provide relief to patients with the pruritus of cholestasis is underscored by the use of invasive procedures that aim to remove hypothetical pruritogens from the circulation. These procedures include charcoal hemoperfusion, plasmapheresis, partial external diversion of bile, and ileal diversion. The nature of any relevant substance(s) removed by these interventions is not known.

### See Also the Following Articles

**Biliary Tract, Developmental Anomalies of the • Bile Formation • Cholestatic Diseases, Chronic • Cirrhosis • Histamine • Liver Transplantation**

### Further Reading

Bergasa, N. V., and Jones, E. A. (1993). The pruritus of cholestasis. *Semin. Liver Dis.* 13, 319–327.

Bergasa, N. V., Mehlman, J. K., and Jones, E. A. (2000). Pruritus and fatigue in primary biliary cirrhosis. *Bailliere Best Pract. Res. Clin. Gastroenterol.* 14, 643–655.

Bergasa, N. V., Liau, S., Homel, P., and Ghali, V. (2002). Hepatic Met-enkephalin immunoreactivity is enhanced in primary biliary cirrhosis. *Liver* 22, 107–113.

Jones, E. A., and Bergasa, N. V. (1995). The pruritus of cholestasis: Potential pathogenic and therapeutic implications of opioids. *Gastroenterology* 108, 1582–1588.

Thornton, J. R., and Losowsky, M. S. (1988). Opioid peptides and primary biliary cirrhosis. *Br. Med. J.* 297, 1241–1242.

# Psychiatric Issues, Overview

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**Crohn's disease** Inflammatory bowel disease of part of or the entire gastrointestinal tract and that extends all the way through the intestinal wall.
**dysmenorrhea** Painful menstruation.
**dyspepsia** Indigestion, upset stomach, or pain or discomfort centered in the upper abdomen.
**dysuria** Painful urination.
**fibromyalgia** Disorder of pain and tenderness of muscle and adjacent connective tissue. Synonyms include fibrositis and fibromyositis.
**functional gastrointestinal disease** Collection of persistent or recurrent gastrointestinal symptoms not known to be caused or produced by any specific morphologic, biochemical, or physiologic abnormalities.
**globus** Sensation of a lump or something stuck in the throat, tightness of the throat, or inability to swallow.
**inflammatory bowel disease** Group of chronic gastrointestinal diseases, including ulcerative colitis and Crohn's disease, involving inflammation of the gastrointestinal tract.
**irritable bowel syndrome** Group of functional gastrointestinal disorders of the bowel in which abdominal discomfort or pain is associated with defecation, or a change in bowel habit and bowel movements, not due to known structural gastrointestinal disease.
**nocturia** Excessive urination at night.
**psychoform** Psychological symptoms suggesting psychiatric disorders that the individual does not have.
**psychosomatic** Bodily symptoms presumed to arise from psychological origins.
**somatization disorder** Psychiatric illness that occurs predominantly in women, characterized by multiple physical complaints throughout the body's organ system without medical explanation.
**somatoform** Physical symptoms suggesting a medical basis but without medical explanation.
**structural gastrointestinal disease** Well-documented associations of disease of the gastrointestinal tract, with observable structural or morphologic changes.
**ulcerative colitis** Inflammatory bowel disease characterized by inflammation of the more superficial layers, the mucosa and submucosa, of the colon.

**The sheer prevalence of psychiatric illness is of considerable significance to all medical practice. In the general population, one in five people suffer from a diagnosable psychiatric illness in any given year, but most do not find their way to treatment. In medical treatment settings, a current psychiatric diagnosis can be made in approximately one out of every three patients, but, in reality, most psychiatric illness goes undetected.**

## SCOPE AND PREVALENCE OF PSYCHIATRIC COMORBIDITY IN GASTROINTESTINAL DISEASE

Recognition of psychiatric illness in gastrointestinal disease is important not only because psychiatric illness is a source of much suffering in itself, but also because it is associated with significant disability, worse medical outcomes, and higher medical care costs. Recognition and treatment of psychiatric disease can significantly reduce medical care costs and can be expected to improve the management of comorbid gastrointestinal disease.

Different gastrointestinal diseases vary in both the prevalence and types of associated psychiatric disorders. In the following discussions, the gastrointestinal diseases are examined separately for their associations with particular psychiatric disorders, focusing on how the different psychiatric comorbidities present special problems of management.

## PSYCHIATRIC DISORDERS IN STRUCTURAL AND FUNCTIONAL GASTROINTESTINAL DISEASE

Functional gastrointestinal (GI) disorders are defined as persistent or recurrent groups of gastrointestinal symptoms not linked to known morphologic, biochemical, or other physiologic abnormalities. Structural gastrointestinal disease, in contrast, presents with objective diagnostic features on physical examination or on organ-specific tests, such as GI imaging. Psychiatric comorbidity in gastrointestinal disease seems to comply with the functional/structural dichotomy, with higher rates of psychiatric disorders—in particular, somatoform disorders and syndromes—co-occurring

 

with the functional disorders. Studies of psychiatric illness in gastrointestinal disease have found strong associations with functional gastrointestinal disorders, especially irritable bowel syndrome and chest pain of presumed esophageal origin, but weak associations with structural gastrointestinal disease. Structural and functional gastrointestinal diseases appear to have different psychiatric comorbidity patterns.

## Psychiatric Illness in Structural Gastrointestinal Diseases

Historically, many of the structural gastrointestinal diseases have been considered to have psychosomatic origins, despite clear evidence of morphologic abnormalities in the gastrointestinal organs affected. Although the term "psychosomatic" has fallen from accepted usage, previously entrenched ideas persist even with empirical data contradicting them. In part, reluctance to move away from previously established ideas may be because hypotheses of psychosocial origins in medical disease cannot be definitively tested to confirm or disprove them.

In particular, peptic ulcer disease and inflammatory bowel disease have a long tradition of presumed psychosomatic origins, and have accumulated the largest literature supporting these ideas. A large psychoanalytically based literature has accumulated that describes the psychological mechanisms thought to produce these diseases, along with other work that describes how these psychological factors might interact physiologically to yield structural changes in the bowel. The research literature supporting the conceptualization of these structural gastrointestinal diseases as psychosomatic, however, is seriously flawed. The work most strongly supporting this view is the most methodologically flawed.

Possibly feeding the assumption of psychosomatic origins to inflammatory bowel disease and peptic ulcer disease is their potential to be mistaken for, or confused with, functional gastrointestinal diseases with clear psychiatric associations, particularly irritable bowel disease and functional dyspepsia. Although the symptom presentations of peptic ulcer disease and functional dyspepsia are identical, somewhere between 50 and 90% of patients presenting with suspected peptic ulcer disease do not show evidence of an ulcer on physical examination. Because these disorders have such different psychiatric comorbidity patterns, observations made in functional disorders cannot be considered applicable to structural disorders of the same organs.

Methodological problems with this literature start with sampling problems, such as sampling bias, lack of confirmation of the diagnosis, and nonseparation of diseases (especially Crohn's disease and ulcerative colitis, which are actually quite different in their associations with psychopathology). Other serious methodological problems in this literature are lack of a comparison group or use of an inappropriate comparison group, such as healthy individuals in the community, and failure to match or control for important confounders, especially gender (because of higher rates of many psychiatric disorders among women). This latter issue is illustrated by the demonstrated prevalence of psychiatric illness in clinical populations with medical disease in general, which runs around one-third. Therefore, to consider a disease to have specific psychiatric associations, one must demonstrate that the associated psychopathology occurs in rates significantly greater than one-third in Western cultures. Measurement problems in these studies include use of assessment instruments without established validity or reliability, failure to apply diagnostic standards, and lack of comparability of methods across studies. Studies using subjective self-report of symptoms or well being by patients confound medically based symptoms of the disease with symptoms originating in functional overlay that subgroups of patients in all populations demonstrate. Therefore, studies documenting a reduction of symptoms with behavioral treatments do not prove psychological origins of the disease, because the results may merely reflect treatment of the functional overlay and not of the disease. Finally, published studies have often drawn conclusions not warranted by the data, and the classic error is assumption of causality from mere association. When two entities statistically occur together, causal relationship may go either direction, or the apparent association may be only indirect through association of both entities with a third variable.

The idea that ulcerative colitis may be a psychosomatic disease first appeared in the scientific literature in 1930, and over several decades a voluminous literature in support of this notion has accumulated. An exhaustive review of the subject found that studies lacking a comparison group were significantly more likely than controlled studies to conclude that ulcerative colitis is psychiatrically based. Looking past the morass of flawed studies, this review proceeded to examine the seven studies with the best methodology. These seven studies all concluded that ulcerative colitis was not distinguishable from other serious medical illnesses in its association with psychopathology.

Crohn's disease is another structural gastrointestinal disease with an established following that holds it to be a disorder rooted in psychological origins. Review of the research literature on this disease reveals the same

kinds of major methodological flaws resulting in unwarranted conclusions based on little evidence. Of 50 original studies examined, only 12 were based on samples of 10 or more subjects. Unlike the best literature on ulcerative colitis, however, the best literature on Crohn's disease overwhelmingly concluded that Crohn's disease was significantly associated with psychiatric illness, on the order of 50% lifetime prevalence. The psychiatric illness consisted largely of major depressive and anxiety disorders. The psychiatric disorders were no more likely to precede than to follow the onset of the Crohn's disease, thus supporting no causal pathway for psychiatric disease in the generation of the gastrointestinal disorder. A study directly comparing Crohn's disease and ulcerative colitis found that the patients with Crohn's disease described poorer psychosocial adjustment, generally reduced well being, and more GI symptoms. Thus, studies suggest that Crohn's disease may be the only structural bowel disease to be associated with psychiatric disorders.

Peptic ulcer disease, probably more than any other structural gastrointestinal disorder, has long been assumed to be a psychosomatic or stress-related condition. Despite this widely held conviction, research shows important distinctions in patterns of psychiatric comorbidity between peptic ulcer disease and other functional gastroduodenal disease. Direct comparison of functional dyspepsia with duodenal ulcer patients found functional dyspepsia to be associated with significantly greater psychopathology (especially anxiety and depression), multiple somatic complaints (especially including dyspepsia symptoms and musculoskeletal symptoms), worse general health, reduced functioning, lower quality of life, and less patient satisfaction with health care received. The patients with duodenal ulcer were older and smoked more often, and almost all were infected with *Helicobacter pylori*. Among duodenal ulcer patients, those with the fewest classic historical risk factors (sex, age, seasonality, family history, smoking, alcohol use, coffee consumption, nonsteroidal antiinflammatory drug use, blood type, serum pepsinogen I, and *H. pylori* antibody titers) had the greatest psychopathology. Thus, it is suggested that clinicians evaluating patients not matching the usual patient profile for duodenal ulcer should be alert for psychologic factors and features suggestive of functional disease instead of, or comorbid with, the peptic ulcer disease. It is important for researchers and clinicians to appreciate that the inevitable occasional psychiatric comorbidity with peptic ulcer disease is not proof of causality from one condition to the other.

Another gastrointestinal disease said to be associated with psychiatric illness is pancreatic cancer. Compared to patients with advanced gastric carcinoma, pancreatic carcinoma patients were found to have higher rates of self-reported depression. The psychiatric findings may be a presenting feature, preceding the diagnosis of cancer. Systematic studies have not been carried out to determine whether it is simple dysphoria or the fully diagnosable syndrome of major depression that precedes the diagnosis of pancreatic cancer. Speculation holds systemic effects of neurotransmitters of the pancreas to be the vehicle for the generation of depressive symptomatology in pancreatic cancer.

## Psychiatric Illness in Functional Gastrointestinal Diseases

Functional gastrointestinal disorders are the most prevalent conditions in gastroenterology practice, constituting up to 50% of presenting problems. Functional gastrointestinal disorders are associated with significant disability, reduced quality of life, and increased medical care costs. Functional gastrointestinal disease is also apparently quite prevalent in the general population, identified in nearly two-thirds (62%) of people assessed by a random telephone survey. In this study, the most prevalent class of functional gastrointestinal disease observed was functional bowel disease (42%), with functional esophageal disease (29%) ranking second and functional anorectal syndromes (23%) ranking third. The most prevalent individual disorders were functional heartburn (22%), functional anorectal pain (17%), functional constipation (15%), abdominal bloating (13%), and irritable bowel syndrome (12%). Even though it ranked only fifth in prevalence among functional gastrointestinal diseases, irritable bowel syndrome is the functional disorder that seems to get the most press.

Functional bowel diseases may overlap with one another diagnostically. This is demonstrated by the documented co-occurrence of functional dyspepsia and irritable bowel syndrome. The functional gastrointestinal syndromes have not been differentiated from one another based on their association with psychopathology. The functional gastrointestinal disease best studied for psychiatric comorbidity is irritable bowel syndrome. Therefore, the following discussion treats the functional gastrointestinal disorders collectively, using irritable bowel syndrome as a model and including research from other functional disorders as relevant to the discussion.

Specific psychiatric disorders have not often been examined together in a single study of irritable bowel syndrome, most studies either focusing on a single disorder or reporting a combined diagnostic rate. The

lifetime prevalence of psychiatric disorders in patients with irritable bowel syndrome has been reported in 72–93%, the most prevalent individual diagnoses being major depression (8–61%), anxiety disorders (4–61%), hysteria (17–28%) or somatization disorder (32–48%), and undiagnosed psychiatric disorder (31–32%). The onset of psychiatric illness precedes the onset of the irritable bowel syndrome in four out of five cases, suggesting that the association does not routinely signify the generation of psychopathology from the bowel disease. Although less thoroughly studied, psychiatric comorbidity in other functional disorders has been found in the ranges reported for irritable bowel syndrome. For functional dyspepsia, psychiatric comorbidity has been reported to be 87%, with anxiety disorders diagnosed in 67%. Psychiatric comorbidity in esophageal spasm was reported as 84%, consisting largely of anxiety disorders, major depression, and somatization disorder.

A specific psychiatric disorder singled out in studies of functional gastrointestinal disease is panic disorder. Panic disorder has been reported in association with four functional disorders: globus (25% lifetime panic disorder), noncardiac chest pain of presumed esophageal origins (24–59% prevalence of panic disorder), functional dyspepsia (no panic disorder), and irritable bowel syndrome (23–29% lifetime panic disorder). Panic disorder was identified as being associated with functional gastrointestinal symptoms in a general population study, but more comprehensive analysis found no special association of panic disorder with functional gastrointestinal symptoms. All other psychiatric disorders were found to be similarly associated with the functional gastrointestinal symptoms. Panic disorder was diagnosed in only 4% of individuals with functional gastrointestinal symptoms, which is two to four times the rates (1–2%) in the general population. This nonetheless represented only a fraction of the overall psychopathology, identified in 48% of individuals with functional gastrointestinal symptoms.

Functional gastrointestinal disease is abundant among patients sampled from psychiatric treatment settings. Irritable bowel syndrome has been diagnosed in 17–42% of panic disorder patients, 37% of generalized anxiety disorder patients, 27% of major depression patients, and 42% of patients with alcohol abuse or dependence. These rates are considerably higher than the 12% prevalence of irritable bowel syndrome reported for the general population, suggesting that the association of psychiatric illness with irritable bowel syndrome in patient populations may possibly reflect treatment-seeking bias. Studies of treatment settings specializing in gastrointestinal disease report greater psychiatric comorbidity in association with functional bowel disease compared to data collected from primary care sources. Examination of the relationship of irritable bowel syndrome and psychiatric illness in the general population, in which treatment bias does not apply, does not uniformly show these conditions to be associated, although the reports have been mixed.

The relatively high rates of somatization disorder reported in patients with functional gastrointestinal disease may well represent underestimates of the prevalence of somatization disorder in relation to functional gastrointestinal disease. The source of underestimation lies with the self-report method of obtaining the medical history through cross-sectional patient interviews. Medical histories of patients with this disorder are prone to inaccuracies stemming from misrepresentation of somatic complaints as medically based and failure to report many previous symptoms for which these patients had sought medical intervention.

Somatization disorder was named for its characteristic multiple complaints of symptoms in multiple organ systems. Patients complain that everything is wrong with virtually all the organ systems in their bodies, yet no medical explanation for the symptoms can be found. The multiple complaints offered by patients with somatization disorder include not just physical symptoms but also psychological symptoms. Patients with somatization disorder attending a university psychiatry clinic were found to complain of more depressive symptoms compared patients with a diagnosis of major depression attending the same clinic, as many manic symptoms compared to patients with bipolar disorder, and as many psychotic symptoms compared to patients with schizophrenia. The psychological profile of patients with somatization disorder on the Minnesota Multiphasic Personality Inventory is characterized by a style of exaggeration in reporting symptoms and high rates of endorsement of symptoms on all clinical scales. Therefore, somatization disorder is not only a somatoform disorder in which patients complain of physical symptoms of medical disorders they do not have, but also a "psychoform" disorder in which they also complain of symptoms of psychiatric disorders they do not have. Based solely on their complaints of multiple psychiatric symptoms, additional psychiatric diagnoses may be attributed to them. It could be that the apparent association of irritable bowel syndrome with psychiatric illness is based simply on the comorbidity of irritable bowel syndrome with somatization disorder, the actual source of the many complaints generating psychiatric diagnoses in these patients.

Because irritable bowel syndrome is a disorder defined completely by subjective patient symptom report,

it is possible that the symptom complaints establishing the diagnosis of irritable bowel syndrome in patients with somatization disorder are merely a part of the many symptom complaints of the somatization disorder. The irritable bowel syndrome identified in these patients may not represent the same condition as the irritable bowel syndrome of patients without somatization disorder.

Patients with somatization disorder describe their symptoms as more severe and complain of them more vocally than do other patients. Patients with this disorder are notoriously difficult to manage in the treatment setting. They also report more medication side effects and encounter more treatment complications than other patients. They may be highly demanding and dramatic. Similar observations have been made about the presentation of irritable bowel syndrome. The amount of overlap of somatization disorder with irritable bowel syndrome in patient populations, however, makes it impossible to separate characteristics of the somatization disorder from those of the irritable bowel syndrome. In the irritable bowel syndrome population, much that is ascribed to irritable bowel syndrome may actually represent manifestations of somatization disorder. The extreme nature of the complaints of patients with somatization disorder embedded in an irritable bowel sample may skew findings in irritable bowel syndrome toward poor outcomes and comorbid psychopathology. Therefore, studies of irritable bowel syndrome must separate patients with somatization disorder from those without, to determine what characteristics are driven by the irritable bowel syndrome rather than by somatization disorder.

Irritable bowel syndrome has been described in association with a number of other functional disorders, both within the gastrointestinal tract and in other organ systems. Functional gastrointestinal disorders such as irritable bowel syndrome or functional dyspepsia have been reported in association with fibromyalgia. The more severe the irritable bowel syndrome, the more likely it is associated with fibromyalgia. Irritable bowel syndrome has also been associated with irritable bladder, functional headaches, backaches, muscle aches, dysmenorrhea, urinary frequency and urgency, nocturia, dysuria, sensation of incomplete bladder emptying, chronic pelvic pain, painful sexual intercourse, other sexual dysfunction, dizziness, sleep disturbances, and chronic fatigue. It also shares overlapping features with temporomandibular joint syndrome, premenstrual syndrome, and mitral valve prolapse. Patients with functional bowel disorders visit primary care physicians for symptoms outside the gastrointestinal tract three times more often compared to healthy individuals. Somatization disorder among patients with functional gastrointestinal disease may well account for the apparent overlap of irritable bowel syndrome with other functional disorders.

## CAUSAL DIRECTIONALITIES IN COMORBIDITY OF GASTROINTESTINAL AND PSYCHIATRIC DISORDERS

In functional gastrointestinal disease, comorbid psychiatric disease is clearly associated. Although it has long been assumed that this comorbidity reflects a psychiatric contribution to the development of the gastrointestinal disorder, there is no empirical database to support this assumption, and the temporal sequence (gastrointestinal disorder first, psychopathology later) in the majority is not consistent with it. Another consideration is a possibility of opposite causal directionality in which the gastrointestinal disorders lead to psychopathology. Although it may seem intuitive that irritable bowel syndrome might engender anxiety and dysphoria that could be construed to be part of major depressive and anxiety syndromes, the somatization disorder associated with functional bowel disease characteristically starts early in life, typically in the decade following puberty, and therefore is an unlikely outcome of irritable bowel syndrome. Further, it is not intuitive that irritable bowel syndrome would generate major psychiatric disorders when the same cannot be demonstrated in severe structural gastrointestinal diseases with significant morbidity and mortality not found in irritable bowel syndrome.

A remaining source of the link between psychiatric illness and functional gastrointestinal disease is that a third variable associated with both the functional gastrointestinal disease and the psychiatric disorder provides an indirect link between them. One candidate to represent this connection is stressful life events, which are speculated to contribute to the development of functional gastrointestinal disease. In particular, sexual abuse has been described as associated with symptoms of irritable bowel syndrome, dyspepsia, and heartburn, is and implicated in the generation of irritable bowel disorder. However, causality of sexual abuse in functional medical disorders has not been documented, and sexual abuse is unlikely to represent a specific etiological factor. A more likely causal connection is somatization disorder, which occurs in a significant proportion of functional bowel disease cases and which is associated with other psychopathology. More research is needed to determine to what degree the characteristics attributed to functional

gastrointestinal disorders actually represent features of the associated somatization disorders, and what remains of functional gastrointestinal disease when somatization disorder cases are removed and the functional gastrointestinal disease population is reexamined.

A third variable link between functional gastrointestinal disease and psychopathology is thought to reside within the neurologic wiring of the brain and gut, which share common neurotransmitter substances and are connected in a brain–gut communication network. The role such systems may play in the association of psychopathology with functional gastrointestinal disease is theoretical, however, and empirical validation is needed.

Unlike functional gastrointestinal diseases, structural bowel diseases are not generally associated with psychopathology beyond the nonspecific associations of psychiatric disorders and chronic medical disease in general. One exception appears to be Crohn's disease, which has been seen to be significantly associated with psychopathology. Although the associated psychopathology in both Crohn's disease and functional gastrointestinal disorders includes major depressive and anxiety disorders, irritable bowel syndrome differs from Crohn's disease in its frequent association with somatization disorder, which in turn may be a large source of the associated anxiety and depression. Therefore, although these two conditions share an association with psychiatric illness, the specific psychiatric comorbidities are very different. Although long-standing in medical lore, assumptions of psychological etiologies of structural bowel disease lack empirical support in the research literature.

## TREATMENT IMPLICATIONS

In consideration of comorbid psychiatric disease in the treatment of gastrointestinal illness, it is important to differentiate major psychiatric disorders, such as major depression, from psychological symptoms, such as dysphoria. Major depression and anxiety disorders constitute serious psychiatric illness associated with significant suffering, disability, morbidity, mortality, poor medical outcome, and increased medical costs. Documented success in satisfactory treatment of major psychiatric disorders dictates active vigilance for psychiatric disorders in the management of medical disorders. Not to be confused with major psychiatric illness, dysphoria and anxiety symptoms may be understandable responses to serious medical illness, or they may be part of many "psychoform" complaints among patients with somatization disorder who are by definition polysymptomatic. It is important to approach both research and clinical management in psychopathology in the context of gastrointestinal disease diagnostically, to make these distinctions, which will drive treatment decisions.

Dysphoria and anxiety associated with gastrointestinal disease in medical practice may be managed by supportive psychotherapy and medical education. Major depression and anxiety disorders respond to treatment with antidepressant and antianxiety medications and psychotherapy. Depressive and anxiety complaints arising from somatization disorder rather than primary major depressive or anxiety disorders are best managed in the context of somatization disorder. Management of somatization disorder involves avoiding the potential for iatrogenic harm to the patient through surgical and invasive diagnostic procedures and abusable medications such as narcotics and benzodiazepines, which these patients often receive inappropriately in response to the magnitude of subjective complaints that are not substantiated by objective findings of disease. Interpretation of stressful life events is best considered in the context of psychiatric diagnosis, with caution in ascribing causal attribution, because association of such events with functional gastrointestinal disorders and psychiatric disorders does not demonstrate etiologic origins. Psychiatric disorders may increase risk of the occurrence of negative life events, and somatization disorder is associated with increased reporting of traumatic events.

Although recognition of the associations of psychopathology, stressful life events, and functional gastrointestinal disease can aid the recognition of functional gastrointestinal disease and psychiatric disorders, treatment should be based on diagnostic assessments rather than on assumption of causality. For example, psychotherapy to solve psychological conflicts surrounding a sexual abuse history based on assumptions of the origins of irritable bowel in the history of abuse is not a logical approach to treatment of the disorder based on empirical research.

## CONCLUSIONS AND SUMMARY

Functional and structural gastrointestinal diseases have been seen to have very different associations with psychopathology. Despite a long history of assumption of psychological origins in many structural gastrointestinal diseases, such as inflammatory bowel disease and peptic ulcer disease, empirical data do identify associations supporting such a relationship. In contrast, functional bowel diseases have been seen to be highly associated with psychopathology, but evidence does not specify a causal relationship. Management of

psychopathology in the context of gastrointestinal illness should be aimed at diagnosis of major psychiatric illness and application of treatment approaches appropriate to the disorders identified.

## See Also the Following Articles

**Colitis, Ulcerative • Crohn's Disease • Duodenal Ulcer • Functional (Non-Ulcer) Dyspepsia • Gastric Ulcer • Irritable Bowel Syndrome • Psychosociology of Irritable Bowel Syndrome**

## Further Reading


Clouse, R. E., and Lustman, P. J. (1983). Psychiatric illness and contraction abnormalities of the esophagus. *N. Engl. J. Med.* 309, 1337–1342.

Guze, S. B. (1984). Psychosomatic medicine: A critique. *Psychiatry Dev.* 2, 23–30.

Helzer, J. E. (1985). Psychiatric aspects of inflammatory bowel disease. *In* "Colon, Rectal, and Anal Surgery: Current Techniques and Controversies" (J. J. Kodner, R. D. Fry, and J. P. Roe, eds.), pp. 329–355. Mosby, St. Louis.

Lenze, E. L., Miller, A., Munir, Z., Pornoppadol, C., and North, C. S. (1999). Psychiatric symptoms endorsed by somatization disorder patients in a psychiatric clinic. *Ann. Clin. Psychiatry* 11, 73–79.

Liss, J. L., Alpers, D. H., and Woodruff, R. A. (1973). The irritable colon syndrome and psychiatric illness. *Dis. Nerv. Syst.* 34, 151–157.

Lubrano, E., Iovino, P., Tremolaterra, F., Parsons, W. J., Ciacci, C., and Mazzacca, G. (2001). Fibromyalgia in patients with irritable bowel syndrome: An association with the severity of the intestinal disorder. *Int. J. Colorectal Dis.* 16(4), 211–215.

Magni, G., diMario, F., and Bernasconi, G. (1987). DSM-III diagnoses associated with dyspepsia of unknown cause. *Am. J. Psychiatry* 144, 1222–1223.

Mayer, E. A., Fass, R., and Fullerton, S. (1998). Intestinal and extraintestinal symptoms in functional gastrointestinal disorders. *Eur. J. Surg.* 583, 29–31.

Miller, A., North, C. S., Clouse, R. E., Alpers, D. H., and Wetzel, R. D. (2001). Irritable bowel syndrome, psychiatric illness, personality, and abuse: Is somatization disorder the missing link? *Am. Clin. Psychiatry* 13, 25–30.

Nimnuan, C., Rabe-Hesketh, S., Wessely, S., and Hotopf, M. (2001). How many functional somatic syndromes? *J. Psychosom. Res.* 51(4), 549–557.

North, C. S., Alpers, D. H., Thompson, S. J., and Spitznagel, E. L. (1996). Gastrointestinal symptoms and psychiatric disorders in the general population: Findings from the NIMH Epidemiologic Catchment Area project. *Dig. Dis. Sci.* 41, 633–640.

North, C. S., Clouse, R. E., Spitznagel, E. L., and Alpers, D. H. (1990). The relation of ulcerative colitis to psychiatric factors: A review of findings and methods. *Am. J. Psychiatry* 147(8), 974–981.

North, C. S., and Guze, S. B. (1998). Somatoform disorders. *In* "Washington University: Adult Psychiatry" (S. B. Guze, ed.), pp. 269–283. Mosby, St. Louis.

Smith, G., Rost, K., and Kashner, T. (1995). A trial of the effect of a standardized psychiatric consultation on health outcomes and costs in somatizing patients. *Arch. Gen. Psychiatry* 52, 238–243.

Wilhelmsen, I., Haug, T. T., Ursin, H., and Berstad, A. (1995). Discriminant analysis of factors distinguishing patients with functional dyspepsia from patients with duodenal ulcer. Significance of somatization. *Dig. Dis. Sci.* 40, 1101–1111.

Young, S. J., Alpers, D. H., Norland, C. C., and Woodruff, R. A. (1976). Psychiatric illness and the irritable bowel syndrome: Practical implications for the primary physician. *Gastroenterology* 70, 162–166.

Yunus, M. B., Masi, A. T., and Aldag, J. C. (1989). A controlled study of primary fibromyalgia syndrome: Clinical features and association with other functional syndromes. *J. Rheumatol. Suppl.* 19, 62–71.

# Psychosociology of Irritable Bowel Syndrome

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**abuse** Threats or actions of an emotional, sexual, or physical nature in which a power differential exists between the perpetrator and the victim.

**antidepressant** A class of drugs, the primary effect of which is to correct neurotransmitter imbalance in the central nervous system occurring in a major depression. Antidepressants tend to be useful in the functional gastrointestinal disorders, both to treat concomitant anxiety and depression and to reduce pain.

**anxiety disorder** Excessive anxiety and worry that cannot be controlled and is persistent with a range of symptoms. Mild forms include phobias; more severe forms include panic disorder.

**biofeedback** The use of electronic or mechanical devices to provide visual and/or auditory information (feedback) on a biological process for the purpose of teaching an individual to control the biological process.

**bulking agents** Macromolecular substances that increase stool bulk and soften feces by water binding. They may be of plant origin (e.g., bran, *Plantago*) or synthetic (e.g., polyethylene glycol). They cannot be split by the enzymes of the human gut, but may be partially digested by the colonic flora.

**depressive disorders** Depression accompanied by reduced activity, reduced appetite, changes in sleep pattern, feelings of fatigue or loss of energy, and feelings of guilt or worthlessness. Suicidal ideas occur in severe forms.

**dualism** A concept, first proposed by Descartes, that separates mind and body. Cartesian dualism (the biomedical model) is the dominant model of illness in Western society and is challenged by the biopsychosocial model.

**health-related quality of life** The impact that illness has on quality of life, including the individual's perception of his or her illness.

Irritable bowel syndrome (IBS) is defined as a group of functional bowel disorders in which abdominal discomfort or pain is associated with defecation or a change in bowel habit. The recently revised Rome II diagnostic criteria for IBS include abdominal pain or discomfort persisting for at least 12 weeks or more that has two or three of the following features: (1) relief with defecation; and/or (2) a change in frequency of stool; and/or (3) a change in form (appearance) of stool. Symptoms associated with IBS include the following: abnormal stool frequency (more than three bowel movements per day or less than three bowel movements per week), abnormal stool form (hard or loose/watery stool), abnormal stool passage (straining or urgency, feeling of incomplete evacuation), passage of mucus, and bloating or feeling of abdominal distension. IBS is estimated to affect 9–22% of the Western population. However, of those affected, very few seek medical consultation or treatment for their gastrointestinal (GI) symptoms. IBS accounts for 28% of gastroenterological practice and 12% of primary care in Western societies. Recent surveys have suggested that individuals with GI symptoms first present to a physician between the ages of 30 and 50 years and there appears to be a decrease in reporting frequency among older adults. Prevalence rates have been found to be similar among Caucasians and African Americans. There have been only a limited number of studies of non-Western ethnic groups but the available reports suggest that IBS appears to be as common in India, China, Japan, and South America as in Western societies. Surveys in the United States indicate that IBS is associated with unnecessary procedures and surgeries and results in over 2.2 million prescriptions per year. In Canada, it is estimated that at least 1.3 million people have IBS, which accounts for over $1.3 billion per year in direct and indirect health care costs. The economic impact of IBS is considerable because in addition to these medical costs, IBS results in decreased work productivity. Next to the common cold, it ranks as the second most common cause of work absenteeism. Furthermore, difficulties in diagnosis and treatment produce uncertainty, frustration, and dissatisfaction within the patient–physician relationship, which can affect patient satisfaction, adherence to treatment, and the clinical outcome.

## BIOPSYCHOSOCIAL MODEL OF IRRITABLE BOWEL SYNDROME

Within a biopsychosocial framework, it is no longer imperative that researchers try to assess whether pain or bowel symptoms are caused by physiological, psychological, or social factors. Rather, the goal of investigators is to determine the extent to which

 

these multiple factors contribute to irritable bowel syndrome (IBS). The research and clinical challenge faced by investigators and clinicians is to determine for each individual the degree to which each of these interacting factors is present and modifiable using a multitude of therapeutic options. Before turning to the specific psychosocial issues that have been identified in the literature on IBS, this article will discuss the stigma associated with IBS and the fact that most of the research to date has focused on one gender when describing psychosocial factors and interventions in IBS.

## STIGMA

Nearly every medical specialty has identified a functional somatic syndrome (FSS). These syndromes are usually defined by physical symptoms unexplained by organic disease. The term "functional" implies a disturbance of physiological function rather than anatomical structure. Functional is often contrasted with organic and is often conceptualized as psychogenic and less "real." The stigma associated with the term functional has resulted in a variety of labels used to describe FSSs, including somatic disorders, health anxiety, physical symptoms unexplained by organic disease, unexplained medical symptoms, and psychophysiological disorders. One of the most common FSSs that have received increased research and clinical attention during the past decade is IBS.

In Western societies in general, and in medicine in particular, there is a moral implication to having a FSS. Underlying the dualistic metaphysics of Western medicine, illness is attributed to impersonal causes or viewed as an accident that befalls the patient as victim or else is viewed as psychologically caused and mediated and potentially under the person's voluntary control. The morally pejorative connotations of a FSS often leave patients believing that their problems are not being treated as real but instead are due to a psychological or moral defect or weakness. Research indicates that disorders disproportionately prevalent in women, such as IBS, are often trivialized or described as psychological in origin. Thus, women may be especially attentive to the possibility that their illness symptoms are not being taken seriously. Accordingly, it is important to highlight that, when a person with IBS is referred to a health care professional, he or she may come into the office with the expectation that the caregiver does not think his or her symptoms are real or serious, but are "all in his or her head." Validating the reality of the person's symptoms and challenging society's view of the artificial dualism of functional/organic components of illness can enhance the therapeutic alliance. The stigma associated with IBS further highlights the need for patients and health professionals to conceptualize IBS within a biopsychosocial framework.

## GENDER

IBS is a disorder that is diagnosed mostly in women. Although men and women are affected by IBS, studies consistently demonstrate that women outnumber men within the nonpatient population, within primary care settings, and within tertiary care settings. To date, most of the information about IBS has been drawn from women research participants. A review of the literature indicated that the majority of studies investigating IBS used only women in their samples. Moreover, among the few studies that did include men, a gender difference analysis was rarely performed. Studies that examined sex differences did so only in a descriptive manner, did not test for statistically significant differences, and sampled only a small number of people. Of those studies that investigated sex differences and included both male and female participants in the sample, the focus was in the areas of frequency of physician visits, psychological symptoms, physical symptoms, and abuse histories. Thus far, the literature suggests that there are few consistent sex differences. However, since a significant percentage of patients with IBS are women, the issue of gender must be integrated into the conceptualization and treatment of this disorder.

## ROLE OF PSYCHOSOCIAL FACTORS

There is an increasing consensus in the literature that specific psychosocial factors are not characteristic of the disorder and thus are not considered as a part of a diagnosis. Nonetheless, psychosocial factors are important to identify in order to help to understand their role in clinical presentation and in planning relevant interventions. It is important to keep in mind that the specific psychosocial factors described below are not unique to patients with IBS but have been reported to occur in other patients with chronic medical conditions. Research on the role of psychosocial factors in IBS has focused on four general areas: anxiety and depression; stress; abuse; and quality of life.

### Anxiety and Depression

A large proportion of patients with IBS manifest concurrent anxiety and/or depression. Research using standardized interviews indicates that among IBS patients in tertiary health centers, the prevalence of a

psychiatric disorder (mainly anxiety and depressive disorders) ranges from 40 to over 90%. Three possible, interrelated, explanations for the association between IBS and anxiety and depression are suggested here. The first is that the co-occurrence of IBS with anxiety and depression may simply be due to overrepresentation of these disorders among women in the general population. A second possible explanation is that people with IBS and an associated anxiety or depressive disorder seek more specialized help than people with IBS without anxiety and/or depression. Thus, the former group may be more likely to enter the health care system because they have more difficulty coping with their IBS symptoms. Finally, it is also possible that IBS may have such a debilitating effect on individuals' lives that anxiety and depression manifest. It is important to note that although the prevalence of anxiety and depressive disorders is overrepresented among the subset of patients seeking health care for their gastrointestinal (GI) symptoms, these disorders are not associated with IBS per se.

### Stress

Stressful events produce GI symptoms in most people but patients with IBS may be particularly susceptible and have a greater reactivity to stress. Among patients with IBS, stress is associated with symptom onset and severity. Moreover, research suggests that patients with IBS report more lifetime and daily stressors when compared with other medical populations or healthy controls. Thus, identifying specific types of stressors, including psychological, social, physical, dietary, and hormonal stressors, that are related to an exacerbation of GI symptoms may be helpful in devising a treatment plan that utilizes appropriate and relevant interventions.

### Abuse

Patients diagnosed with functional bowel disorders are significantly more likely than patients with organic bowel disorders to have had a history of forced intercourse and to have experienced frequent physical abuse. Moreover, female patients with functional GI disorders are more likely to have experienced life-threatening physical abuse and to have been victims of rape in their lifetime when compared with control group female patients. Studies indicate that a history of physical or sexual abuse among patients with functional GI disorders contributes to poor health status. Specifically, women who have experienced abuse are more likely than women who have not experienced abuse to complain about pelvic pain, headaches, backaches, fatigue, and joint pain to their physicians.

Sexual abuse, in particular, may act as a nonspecific but severe psychological stressor, increasing physiological arousal and thereby triggering or exacerbating a patient's GI symptoms. However, despite the strong evidence regarding the prevalence and ramifications of physical and sexual abuse, few studies to date have examined the impact of emotional abuse among patients with IBS. In one recent study, emotional abuse was found to be significantly more prevalent in the women with IBS seen at tertiary centers than in the women with organic bowel disorders. Using a qualitative, semistructured interview, it was found that a large number of women with IBS perceived that past physical, sexual, or emotional abuse played an important role in the precipitation and/or exacerbation of their GI symptoms.

### Quality of Life

Research suggests that patients with IBS have significantly poorer health-related quality of life than the general population or other patient groups (such as diabetes and end-stage renal disease). When compared with patients having other GI conditions, physical, emotional, and social role functions and energy were poorer among patients with IBS. However, this general finding is qualified such that the degree of impairment among people with IBS relates to the target population studied. Specifically, nonpatients with IBS have health-related quality of life scores that are intermediate between referred IBS patients and nonpatient control groups. When using questionnaires specific to IBS, patients fare the worst in terms of food avoidance, activity interference, and health worry concern. It was also found that quality of life improves in relation to changes in pain severity and daily function after psychological or antidepressant treatment.

## PSYCHOSOCIAL INTERVENTIONS

In general, controlled studies have demonstrated the effectiveness of treating IBS with cognitive-behavioral therapy, relaxation training, hypnosis, and dynamic/interpersonal therapy. Since most of the research to date has focused on cognitive-behavioral therapies, this section is discussed in more detail relative to the other therapies.

### Cognitive-Behavioral Therapy

Cognitive-behavioral techniques consist of a wide range of strategies and procedures designed to bring

about alterations in patients' perceptions of their situation and their ability to control their GI symptoms. The focus in cognitive-behavioral therapy (CBT) is on exploring how certain cognitions and behaviors may affect GI symptoms and associated psychosocial distress.

There have been 12 controlled studies including cognitive-behavioral or cognitive techniques in the treatment of IBS. Most of these techniques have been used within a multicomponent cognitive-behavioral treatment package. Treatment packages have included various combinations of cognitive therapy, stress management training, contingency management, relaxation techniques, psycho-educational components, assertiveness training, pain management, and bowel habit training. A significant amount of evidence supports the efficacy of CBT in relieving IBS symptoms and psychological distress (namely, depression and anxiety) relative to control conditions, such as waiting list control group, antispasmodics and bulking agents control group, symptom-monitoring control group, attention placebo control group, and psycho-educational control groups. A brief summary of findings from CBT packages will be presented by control group. Compared to a waiting list control group, one study found that CBT improved abdominal symptoms, coping strategies, and avoidance behavior. Several studies have found that CBT resulted in superior or similar improvement in GI symptoms when compared to the use of antispasmodics and/or bulking agents. Studies that compared CBT to symptom-monitoring controls found that CBT treatment packages improved GI symptoms and psychological distress relative to controls. One study indicated that CBT group therapy improved depressive symptoms and bowel symptom diary scores. Similar improvements were not found in the psycho-educational group. Finally, studies using cognitive therapy found significant improvement in IBS symptoms, depression, and anxiety relative to symptom monitoring and significant improvement in IBS symptoms and depression relative to an attentional-placebo control.

## Relaxation Training

Relaxation or arousal reduction techniques encompass a variety of different methods used to teach patients how to counteract the physiological sequelae of stress or anxiety. The rationale for these techniques is premised on the belief that if muscle tension or autonomic arousal decreases, subjective anxiety or tension will also decrease as a consequence. The most common arousal reduction techniques include progressive muscle relaxation training, biofeedback for striated muscle tension, skin temperature, or electrodermal activity, autogenic training, and transcendental or Yoga meditation.

These techniques are typically combined with other treatments, making it difficult to determine the precise contribution of relaxation training. Moreover, support for the efficacy of any one relaxation training technique for the treatment of IBS is inconclusive. One study that did evaluate progressive muscle relaxation alone found greater reductions in IBS symptoms when compared with the symptom-monitoring control group. However, other research indicates that specific biofeedback to modify colon contractions was not effective for IBS even though generalized biofeedback with other relaxation techniques has been used successfully.

## Hypnosis

The hypnotic "state" is one of heightened suggestibility. Following induction, the hypnotherapist uses progressive muscular relaxation plus suggestions of relaxation to reduce striated muscle tension. "Gut-directed" imagery and suggestions are used to relax GI smooth muscle. Hypnotherapy sessions end with the patient being told that he or she will feel positive and good about himself or herself. Patients are also asked to practice autohypnosis at home with an audiotape, with the ultimate goal of being able to administer suggestions of relaxation to themselves.

Studies on hypnotherapy have found that hypnosis results in a reduction of abdominal pain and altered bowel habits that can be maintained for at least 18 months. Improvements in quality of life, psychological symptoms, and rectal pain sensitivity have also been found.

## Dynamic/Interpersonal Therapy

Dynamic or interpersonal psychotherapy is derived from psychodynamic principles and integrates humanistic and interpersonal concepts. This approach differs, however, from that of traditional psychoanalysis by moving away from the asymmetrical relationship between the therapist and the patient. Dynamic/interpersonal psychotherapy is most suitable for patients with problems stemming from difficulties in interpersonal relationships.

There are few studies on this form of therapy. The available evidence on dynamic/interpersonal therapy is supportive. Compared to the control conditions, dynamic/interpersonal psychotherapy led to greater reductions in bowel symptoms and psychological symptoms. Improvements were sustained at long-term follow-up.

As a final note on psychosocial interventions, regardless of the approach, a good working partnership between the person with IBS and his or her health care

professional is integral to success. Health care professionals must recognize that individuals with IBS can provide expertise on the factors that aggravate their bowel symptoms. Moreover, patients with IBS can rightly expect health care professionals to collaborate with them in understanding and managing their condition. As with many other illnesses, IBS can be influenced by psychosocial factors interacting with biological processes. Educating health care professionals and general society about the multidimensional nature of IBS can help toward conceptualizing multiple treatment approaches and developing a collaborative partnership between the patient and the health care professional.

## FUTURE DIRECTIONS

This article has reviewed evidence pointing to the importance of psychological and sociological factors in IBS; however, further research is still required using a biopsychsocial perspective. Some possible avenues that this research might take are as follows: More research is needed to fully understand the influence of gender and sociocultural factors and the influence of clinical setting (e.g., nonpatients, primary care, GI referral, psychiatric referral) on IBS. Studies that will standardize current measures and develop new instruments for functional GI disorders are needed in order to examine interactions between psychosocial variables and bowel symptoms. Moreover, outcome measures that focus on clinically meaningful responses, such as satisfaction with treatment, health-related quality of life, global well–being, and coping with symptoms, should be further refined and incorporated into clinical trials.

Much research is still needed in the domain of treatment for IBS. A recent review of the literature on psychosocial treatment for IBS pointed to some key issues that should be addressed in the future. First, more attention should be focused on the distress associated with living with a chronic, debilitating illness. Society has continued to stigmatize patients with these disorders, trivializing their symptoms and treating them with a lack of empathy. To date, little theoretical or empirical work has been directed toward identifying and integrating the concerns of IBS patients into treatment plans. As a result, few psychosocial approaches have been tailored to the specific needs of people suffering from IBS. Second, studies must be designed to overcome the methodological limitations of previous investigations in this area. Psychosocial intervention studies should improve upon previous methodology by: including specific selection criteria for IBS; stratifying patients by symptom severity; enrolling sufficient numbers of female and male patients; including sufficient documentation of treatment plans to allow standardization and replication of treatment protocols; including session-by-session treatment manuals and measures of therapist adherence to treatment protocols; using appropriate placebo conditions to address expectancy and attention; and measuring credibility to treatment condition.

Further studies are required to determine the characteristics of patients, which predict response to specific psychosocial treatments and the specific components of psychosocial treatment packages (e.g., relaxation and cognitive restructuring), which account for their effectiveness. In addition, well-designed, randomized, controlled trials that offer a more holistic bi psychosocial approach are needed. In particular, there is growing evidence in this field that certain combination treatments that address both biological and psychosocial aspects may have synergistic effects (CBT plus antidepressant medication). Treatment studies can help clinicians to understand the effect of physician communication skills on patient satisfaction with care, adherence to treatment, and outcome.

### See Also the Following Articles

**Irritable Bowel Syndrome • Psychiatric Issues, Overview • Stress**

### Further Reading

Ali, A., Toner, B. B., Stuckless, N., Gallop, R., Diamant, N. E., Gould, M. I., and Vidins, E. I. (2000). Emotional abuse, self-blame, and self-silencing in women with irritable bowel syndrome. *Psychosomatic Med.* 62, 76–82.

Drossman, D. A., Corazziari, E., Talley, N. J., Thompson, W. G., and Whitehead, W. E. (eds.) (2000). "Rome II: The Functional Gastrointestinal Disorders," 2nd Ed. Degnon Associates, McLean, VA.

Drossman, D. A., Creed, F. H., Olden, K. W., Svedlund, J., Toner, B. B., and Whitehead, W. E. (1999). Psychosocial aspects of the functional gastrointestinal disorders. *Gut* 45, II25–II30.

Drossman, D. A., Mayer, E. A., Camilleri, M., and Whitehead, W. E. AGA technical review on irritable bowel syndrome. *Gastroenterology*, in press.

Toner, B. B., and Akman, D. E. (2000). Gender issues in irritable bowel syndrome. *Am. J. Gastroenterol.* 95, 11–16.

Toner, B. B., Segal, Z. V., Emmott, S. D., and Myran, D. (2000). "Cognitive-Behavioral Treatment of Irritable Bowel Syndrome: The Brain–Gut Connection." Guilford, New York.

Toner, B. B., Segal, Z. V., Emmott, S. D., Myran, D., Ali, A., DiGasbarro, I., and Stuckless, N. (1998). Cognitive-behavioral group therapy for patients with irritable bowel syndrome. *Int. J. Group Psychother.* 38, 215–243.

# Pylephlebitis

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**pylephlebitis** Suppurative endophlebitis of the portal venous system.
**pylethrombosis** Thrombosis of the portal venous system.

**Acute suppurative pylephlebitis is septic thrombophlebitis of the portal venous system, a rare entity first described in the late nineteenth century in association with appendicitis. With early surgical intervention and antibiotics in patients with appendicitis, the overall incidence has decreased, and other pyogenic processes draining into the portal circulation or arising in close proximity have become more prominent as predisposing conditions. Original reports noted 100% mortality, which has decreased with modern therapy. Despite these improvements, suppurative pylephlebitis remains a serious life-threatening development. Most case series in the literature are small subgroups of larger series of either pyogenic liver abscess or pylethrombosis, making conclusions regarding proper therapy difficult.**

## ETIOLOGY

Most cases of pylephlebitis are due to a primary infectious process in the abdomen or pelvis. Diverticulitis is the most common cause, accounting for 32% of 19 cases in a recent review of the literature since 1979 by Plemmons. Malignancy, particularly of the biliary tree, has accounted for a larger number of cases in more recent reviews, and some researchers suggest that more aggressive treatment of advanced biliary cancers may account for the increase. Appendicitis still accounts for a significant portion of pediatric cases, and inflammatory bowel disease, pancreatitis, cholangitis, endometritis, hemorrhoidal disease, peptic ulcer disease, and Behçet's disease have all been reported causes. Suppurative pylephlebitis may also develop secondarily as a complication of bacteremia with coexistent portal vein thrombosis.

## MICROBIOLOGY

Gut flora, particularly *Escherichia coli*, *Proteus mirabilis*, and *Bacteroides fragilis*, are the predominant pathogens isolated from blood cultures and aspirations. A significant portion of infections are polymicrobial. In Plemmons' series, *B. fragilis* was the single most common species isolated from blood. Less common reported isolates include *Fusobacterium nucleatum*, *Gardnerella*, and *Candida albicans*.

## CLINICAL MANIFESTATIONS

Symptoms are nonspecific, including fever, abdominal pain, chills and rigors, jaundice, and anorexia. Symptoms relating to the primary infectious process may be absent. Diagnosis relies on a high index of suspicion given the protean nature of the history and physical examination findings. Hepatomegaly may be present, and jaundice occurs less often and later than in cholangitis, and becomes more likely if liver abscesses develop. Leukocytosis is a prominent, albeit nonspecific, feature. Blood cultures are positive in 88% of cases. Radiology is the mainstay of diagnosis. Plain films are insensitive but may reveal air in the portal tree. Ultrasound with Doppler may indicate obstruction to portal venous flow. Computer tomography (CT) with intravenous contrast injection offers the advantage of evaluating the pylephlebitis and diagnosing the primary infectious focus, as well as complications such as liver abscess. Characteristic findings include lack of the expected contrast-opacified portal veins, intravascular air, and clots. Cavernous transformation, well described in subacute nonsuppurative pylethrombosis, may not be present in acute cases. Angiography has been used but has significant complications. Magnetic resonance angiography may in time provide a low-risk tool.

## COMPLICATIONS

Pyogenic liver abscesses occur in about 50% of cases of pylephlebitis, and about 15% of pyogenic liver abscess cases demonstrate pylephlebitis. Bacteremia is present in 88% of cases, and sepsis, occurring in 21% of patients, remains the most common and serious threat. Mesenteric ischemia is rare but catastrophic. Reported mortality in the older literature in the antibiotic era was 50%; for more modern cases, 32% mortality is reported for all

 

etiologies, but in one review it is 80% for nonappendiceal cases. Several researchers have noted higher mortality for cases attributed to diverticulitis.

## TREATMENT

No controlled studies exist, and limited case series differ widely in treatment modalities and recommendations. All agree that the mainstay of therapy is immediate antibiotics with activity against coliforms, enterococci, and anaerobes, which may be modified based on the results of search for the primary infectious source and on culture data. Typical recommendations are for 4–6 weeks of therapy at a minimum, with an initial period of intravenous therapy followed by a number of weeks of oral therapy. Followup CT may be helpful, but complete resolution of CT findings will lag behind microbiologic cure. Some researchers recommend followup imaging to document resolution of the thrombus, inasmuch as late presentations of complications of portal vein thrombosis have been reported.

Anticoagulation remains controversial due to reports of recanalization of the portal vein without intervention, and no clear evidence of benefit. One case series of 44 heterogeneous patients suggested improved outcomes in the few patients with underlying hypercoagulable states who received anticoagulation, and no adverse effects secondary to the anticoagulant therapy. However, in the absence of a documented hypercoagulable state, many researchers do not recommend anticoagulation. An important point is the paucity of reported deaths due to progression of mesenteric ischemia or embolization of clot. Most deaths occur due to infection-related complications. Several reports exist of CT-guided percutaneous drainage in selected patients, and surgical drainage may be required. Thrombolytic therapy has been considered contraindicated by some researchers due to the possible need for emergent surgical intervention, but a few reports of success exist.

## See Also the Following Articles

**Appendicitis • Computed Tomography (CT) • Liver Abscess • Portal Vein Thrombosis**

## Further Reading

Balthazar, E. (2000). Septic thrombophlebitis of the mesenteric and portal veins: CT imaging. *J. Comput. Assist. Tomogr.* 24(5), 755–760.

Pelsang, R. (2001). Management of suppurative pylephlebitis by percutaneous drainage: Placing a drainage catheter into the portal vein. *Am. J. Gastroenterol.* 96(11), 3192–3194.

Plemmons, R., Dooley, D., and Longfield, R. (1995). Septic thrombophlebitis of the portal vein (pylephlebitis): Diagnosis and management in the antibiotic era. *Clin. Infect. Dis.* 21(5), 1114–1120.

Saxena, R., Adolph, M., Ziegler, J., Murphy, W., and Rutecki, G. (1996). Pylephlebitis: A case report and review of outcome in the antibiotic era. *Am. J. Gastroenterol.* 91(6), 1251–1253.

Setto, R., and Rockey, D. (1996). Pyogenic liver abscess. Changes in etiology, management, and outcome. *Medicine* 75(2), 99–113.

# Pyloric Stenosis

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**gastric outlet obstruction** Near-complete or complete blockage of the pyloric channel connecting the stomach to the duodenum, manifesting as early satiety and vomiting of undigested food in adults and projectile, nonbilious vomiting in children. Serum electrolytes may reveal a hypochloremic, hypokalemic alkalosis due to loss of $H^+$ and $Cl^-$ in the vomitus, with compensatory renal secretion of $K^+$ in exchange for $H^+$. In adults, peptic ulcer disease is the most common etiology; in children, pyloric stenosis is most common, with other less frequent causes being pyloric atresia, gastric duplication, and ectopic pancreatic tissue.

**gastroesophageal reflux disease** Clinical syndrome that includes a variety of symptoms and tissue injury associated with abnormal esophageal exposure to regurgitated gastric contents. Long-term complications of consist of erosion ulcers, stricture, Barrett's metaplasia, and esophageal adenocarcinoma. In children, gastroesophageal reflux disease is a significant entity in the differential diagnosis of pyloric stenosis.

**hyperplasia** Growth characterized by an increase in the number of cells.

**hypertrophy** Growth characterized by an augmentation of cell volume.

**pyloric stenosis** Acquired condition involving the thickening of the circumferential muscle of the pyloric sphincter, which results in elongation and obliteration of the pyloric channel. The condition is the most common cause of gastric outlet obstruction in children and is one of the most frequent conditions requiring operation in the first month of life.

**pyloric traumamyoplasty** Alternative operative approach to pyloric stenosis involving the use of a Babcock clamp to grasp and pinch the hypertrophied pyloric muscle, creating two lateral slits on the superior and inferior edges. Results with this technique have been shown to be similar to results with the traditional Ramstedt procedure.

**Ramstedt extramucosal pyloromyotomy** Standard operative approach to pyloric stenosis; involves grasping the pylorus, incising the serosa longitudinally, and spreading or dividing the thickened pyloric muscle until the mucosa is bulging between the separated halves of the pylorus.

**Pyloric stenosis, or hypertrophic pyloric stenosis, is an acquired condition involving the thickening of the circumferential muscle of the pyloric sphincter, which results in elongation and obliteration of the pyloric channel. A near-complete gastric outlet obstruction is produced with secondary dilation, hypertrophy, and hyperperistalsis of the stomach. The observed thickening of the smooth muscle is a result of hypertrophy, not hyperplasia. Pyloric stenosis is the most common cause of gastric outlet obstruction in children and is one of the most frequent conditions requiring operation in the newborn.**

## INTRODUCTION

Sabricius Hildanus first described pyloric stenosis in 1627. Subsequently, Blair described an infant with clinical as well as postmortem findings consistent with hypertrophic pyloric stenosis. Although sporadic reports of children with gastric outlet obstruction in Europe and the United States followed the initial description, the disease was not accepted as a true entity until the description in 1888 of two cases by Hirschsprung, who described it as a congenital disease representing the failure of the involution of the fetal pylorus and named it *angeborener pylorusstenose* (congenital pyloric stenosis). At this time, the preferred treatment was medical, using a combination of gastric lavage, antispasmodic drugs, dietary modifications, and the local application of heat, secondary to a 100% surgical mortality rate. Lobker performed the first successful surgical procedure to treat an infant with pyloric stenosis, using a gastrojejunostomy to bypass the obstructed pylorus. Unfortunately, the overall mortality for this procedure at that time remained high, approximately 50–60%. Nicoll and Fredet, in 1906 and 1907, each independently described a technique of longitudinal submucosal division of the thickened pyloric muscle with transverse suturing of the defect (pyloroplasty). This type of extramucosal pyloroplasty was unsatisfactory, due to excessive hemorrhage, which occurred when sutures tore through the edematous muscle that had been closed. In 1912, Ramstedt simplified the Fredet procedure by omitting the transverse suturing, which leaves the mucosa exposed in the longitudinal seromuscular defect. Not only was the procedure successful, but its essential elements have remained generally unmodified and remain the surgical standard.

 

Pyloric stenosis is the most common cause of gastric outlet obstruction in children. The prevalence of pyloric stenosis ranges from 1.5 to 4 in 1000 live births among Caucasians but is less prevalent in Asians, Hispanics (1.8 per 1000 live births), and African-Americans (0.7 per 1000 live births). Multiple reports have suggested that the incidence may be increasing. For instance, a United Kingdom population-based study has documented a rise in incidence from 0.1–0.2% up to 0.3–0.8% during the past several decades. Additionally, at the Mayo Clinic, a large population-based study has documented an overall incidence of 0.26% in Olmsted County, Minnesota, from 1950 to 1984, but showed that the rate approached 0.5% by the end of the study period. It is well known that pyloric stenosis is more common in males than females, with a ratio of 2:1 to 5:1, although the long-held belief that it primarily affects first-born males has not been confirmed.

The development of pyloric stenosis has been associated with several variables, including both environmental and familial factors. A genetic contribution is supported by the fact that 19% of boys and 7% of girls whose mothers had pyloric stenosis also have the disease. Pyloric stenosis occurs in only 5% of boys and 2.5% of girls whose fathers have the disease, suggesting some type of variable maternal transmission. Additionally, the risk of pyloric stenosis is lower with older maternal age, higher maternal education, and low birth weight.

Generally, a majority of patients with pyloric stenosis are felt to have an acquired defect, with or without a preexisting genetic predisposition. One supportive study examined a series of 1000 males with barium swallow immediately after birth, finding no abnormalities of the pylorus. Subsequently, 5 of those infants went on to develop pyloric stenosis. In a second study, 1400 randomly selected newborn infants underwent ultrasonographic measurements of the pylorus, revealing normal pyloric dimensions; 9 infants (0.65%) later developed pyloric stenosis. On the other hand, as many as 7% of infants with pyloric stenosis have associated malformations, including intestinal malrotation, obstructive uropathy, and esophageal atresia. Other anomalies associated with pyloric stenosis include hiatal hernia and a deficiency in hepatic glucuronyl transferase activity.

## ETIOLOGY/PATHOPHYSIOLOGY

The cause of pyloric stenosis remains poorly understood, but several hypotheses have emerged. Family history, sex, and maternal feeding patterns, among others, have all been deemed potential risk factors. In addition to the variability among races and the clear male predominance, there appears to be an increased risk with a positive family history and certain ABO blood types. Environmental factors associated with pyloric stenosis include the feeding method (breast vs. formula feeding), seasonal variability, and transpyloric feeding in premature infants. An association between systemic erythromycin in infants and subsequent pyloric stenosis has also been investigated. Although numerous theories have been proposed, none has received generalized acceptance.

Some investigators have suggested that milk curds in the stomach could obstruct the pyloric channel or produce edema of the pyloric mucosa and submucosa, obstructing the pyloric channel, leading to compensatory hypertrophy of the pyloric muscle. Others have focused on pyloric muscle innervation and relaxation. Different investigators have found that the numbers of ganglion cells in the pylorus and/or their maturity have been abnormal, although these results have not consistently been reproduced. Specifically, a markedly decreased number of glial-derived growth factor-positive nerve fibers has been found in patients with pyloric stenosis, as well as a reduced production of neurotropins. Confocal microscopy studies have shown the presence of abnormally thick contorted nerve bundles in the pyloric muscle of infants with pyloric stenosis. Others have investigated a lack of nitric oxide synthase in pyloric tissue as being a potential contributor to pylorospasm, possibly leading to pyloric stenosis, because nitric oxide is a known muscle relaxant.

Further hypotheses involve levels of gastrointestinal endocrine or paracrine factors. Various investigators have shown that gastrin is elevated in patients with pyloric stenosis and may be a stimulus toward muscle hypertrophy. On the other hand, hypergastrinemia and hyperacidity are known to occur secondary to gastric outlet obstruction from any cause. Furthermore, these patients have been shown to have elevated prostaglandins as well. Infants receiving infusions of certain prostaglandins have been shown to develop gastric outlet obstruction, but have not gone on to develop pyloric stenosis. Substance P has been shown to produce chronic pylorospasm, leading to muscle hypertrophy, and has also been found in higher concentrations in the pyloric muscle of patients with pyloric stenosis. Other peptides, such as secretin, enteroglucagon, neurotensin, and vasoactive intestinal peptide (VIP), have also been linked to pyloric stenosis, although their exact roles have yet to be elucidated. Furthermore, elevated levels and expression of transforming growth factor-α (TGF-α) and epidermal growth factor (EGF) mRNA have been

found in infants with pyloric stenosis, although the significance is unclear. Currently, the cause of pyloric stenosis has not been definitively elucidated and appears to be multifactorial, although considerable basic science investigations are ongoing.

## CLINICAL PRESENTATION

Typically, an infant with pyloric stenosis presents with a normal feeding history and new onset of nonbilious, emesis at 2 to 8 weeks of age, with a peak incidence of 3 to 5 weeks. Initially the emesis may not be frequent or forceful, but becomes progressively worse over days until nearly every feeding is forcefully vomited in a "projectile" fashion. Less frequently, the emesis may be blood tinged or have a coffee-ground appearance due to gastritis or esophagitis. Generally, infants appear hungry immediately after vomiting and do not appear ill early in the disease course. Typically, stool frequency is concomitantly diminished. If there is a significant delay in diagnosis, severe dehydration and lethargy can occur. Some children have diarrhea, complicating the diagnosis. Others (2–5%) may have jaundice secondary to glucuronyl transferase deficiency. In premature infants, the presentation is commonly delayed and occurs about 2 weeks later compared to full-term infants; often there is a slower progression of emesis.

The differential diagnosis for pyloric stenosis includes gastroesophageal reflux and formula intolerance, although these usually present with a more gradual onset of emesis. However, a more frequent cause of nonbilious vomiting in the first several weeks of life is either overzealous volume or frequency of feedings (especially formula) offered to the infant. Other causes of nonbilious vomiting include medical disorders such as sepsis, hydrocephalus, and metabolic diseases, as well as entities often requiring surgical intervention, such as antral webs, pyloric atresia, gastric duplication, microgastria, and ectopic pancreatic tissue.

## DIAGNOSIS

The cardinal features of pyloric stenosis include nonbilious projectile vomiting, visible peristaltic waves in the left upper abdomen, a palpable "olive" or enlarged pylorus, and an associated hypochloremic or hypokalemic metabolic alkalosis. These features are more prominent when the diagnosis is delayed, and more subtle earlier in the course. Generally, a definitive diagnosis can be made on the basis of clinical presentation and careful physical examination in as many as 80% of patients, although an increasing reliance on imaging modalities has been seen in the current era of managed care. A recent study has shown that the number of patients diagnosed solely by clinical examination has been decreasing (from 74%, decreasing to 28%), and that the use of diagnostic tests has increased (ultrasonography increasing from 16 to 65% and upper gastrointestinal imaging increasing from 12 to 28%). Several maneuvers can increase the sensitivity of physical examination in pyloric stenosis. The infant must be calm and cooperative and use of a pacifier and warm blanket may be helpful. Additionally, decompression of the stomach with a nasogastric tube may aid in the palpation of the "olive." The examiner standing on the infant's left side should flex the baby's hips with the left hand and palpate the liver edge from above with the right hand. Gentle pressure is applied deep to the liver, and eventually the palpating fingers are moved distally to find a palpable pylorus that can be rolled under the fingertips, making the diagnosis. Examination by a surgeon before imaging studies can be cost effective, with a specificity of 90%, but a sensitivity of only 50%.

In the absence of a palpable mass, an upper gastrointestinal contrast study or ultrasound can usually confirm or dispute the diagnosis. In most pediatric centers, abdominal ultrasound is the study of choice. This technique has a sensitivity of 97%, a specificity of 100%, and a positive and negative predictive value of 100 and 98%, respectively, and has been studied extensively by numerous groups. Its main limitations are operator dependence and the inability to diagnose other causes of nonbilious vomiting. Measurements found to have greater than 90% positive predictive value include a muscle diameter of 17 mm or more, a muscular wall thickness of 4 mm or greater, and a channel length of 17 mm or greater. One group concluded that a muscle thickness of 3 mm should be considered a positive finding for pyloric stenosis in children less than 30 days of age. Last, when measurements are equivocal, calculation of the pyloric volume has been reported to be more accurate.

In the past, an upper gastrointestinal tract series was the gold standard diagnostic study for pyloric stenosis. The test is sensitive and is also helpful in indicating other causes of nonbilious emesis, such as gastroesophageal reflux disease, gastric atony, and delayed gastric emptying. It will also diagnose the dreaded malrotation. The classic radiographic contrast findings are the "string sign," produced by contrast medium outlining the narrowed pyloric channel, and the "shoulder sign," caused by the hypertrophied muscle protruding into the gastric lumen. The pyloric channel may also appear as two parallel threads resembling railroad tracks. A potential disadvantage is that the study exposes the patient to ionizing radiation and involves filling the obstructed

stomach with barium before induction of general anesthesia, increasing the risk of vomiting and aspiration. Therefore, it is recommended that as much of the contrast agent as possible be removed prior to induction of anesthesia.

One suggested means to select the optimal imaging test for pyloric stenosis is to measure the volume of the gastric aspirate obtained by a nasogastric tube. If less than 10 ml is obtained, an upper gastrointestinal tract series may be warranted, because 86% of such infants have been shown to have gastroesophageal reflux disease (GERD). If more than 10 ml is suctioned, an ultrasound examination of the pylorus should be obtained, because 92% of such infants will have pyloric stenosis.

## PREOPERATIVE MANAGEMENT

Once the diagnosis has been made, preoperative preparation is essential, because pyloric stenosis is not a surgical emergency. The child with an early presentation without dehydration, with normal serum electrolyte and glucose concentrations, and normal urine output may be operated on at the earliest convenience. Infants who present with clinical dehydration, including dry mucous membranes, depressed fontanels, increased skin tenting, and varying degrees of malnutrition, require more extensive resuscitation. They characteristically have a hypochloremic, hypokalemic metabolic alkalosis with some degree of hyponatremia and hypoglycemia. One group has defined three levels of severity based primarily on the carbon dioxide content (slight, <25 mEq/liter; moderate, 26–35 mEq/liter; and severe, >35 mEq/liter). Most infants require resuscitation for less than 24–48 hours prior to operation. Initial resuscitation often begins with normal saline or lactated Ringer's solution in boluses of 10–20 ml/kg. A continuous infusion of 5 or 10% dextrose in 0.45% saline is then started at 1.5 times maintenance. Potassium is added after urine output is established. Once the correction of dehydration and restoration of near-normal serum potassium and chloride levels are achieved, as well as correction of the alkalosis to a serum bicarbonate level of below 30 mEq/liter, the operation can be safely conducted. Failure to correct the alkalosis adequately preoperatively can result in postanesthetic apnea and respiratory arrest.

Most infants with pyloric stenosis do not have a complete gastric outlet obstruction and can handle their gastric secretions. Oral feedings are discontinued, but a nasogastric tube is not routinely placed other than temporarily for diagnostic purposes, because it removes additional fluid and acid from the stomach, exacerbating the metabolic alkalosis.

## OPERATIVE MANAGEMENT

The Ramstedt extramucosal pyloromyotomy has long been the classic surgical approach to pyloric stenosis. The standard approach is a right upper quadrant transverse incision of 2.5–3 cm over the right rectus muscle at or above the liver edge. The rectus muscle is either divided or split longitudinally, and the peritoneal cavity is entered through the posterior rectus sheath. The pylorus may be identified by bringing the greater curvature of the stomach through the incision and using it to externalize the pylorus. The serosa on the anterior wall of the pylorus is incised from just proximal to the pyloric vein to the antrum just proximal to the area of hypertrophied muscle. The duodenal end is usually identified by the color change from the pale pylorus to the pink duodenal wall, as well as by the prominent pyloric vein. The myotomy is performed using the back of a scalpel handle to split the hypertrophied muscle bluntly down to the submucosa, or by using a spreading clamp, such as that described by Benson. Once the submucosa is exposed, the overlying muscle fibers should be spread more widely, allowing the submucosa to herniate or bulge out. When the two halves of the pylorus can be moved independently back and forth in opposite directions by a rocking motion, the extent of the pyloromyotomy is complete (Fig. 1). Venous congestion caused by delivering the pylorus through a relatively small incision can result in bleeding from the muscle and submucosa, but generally resolves when the pylorus is returned to the abdominal cavity. Inspection to assure hemostasis should occur before closing the incision.

If the submucosa or mucosa is violated, management is individualized by one of two fundamental techniques. If perforation occurs early in the myotomy, the mucosa is often closed with fine absorbable sutures and the muscle is closed. A second myotomy can then be performed by rotating the pylorus 180°. If the injury occurs when the myotomy is finished, the perforation can be closed and the injury site covered with omentum. Postoperatively, some surgeons decompress the stomach with a nasogastric tube whereas others withhold feedings for a few days. At the end of an uncomplicated pyloromyotomy, some surgeons opt to check for leaks by filling the stomach with 60–100 $cm^3$ of air.

Some surgeons prefer a supraumbilical, curvilinear incision, due to its superior cosmetic results, although there have been reports of a higher incidence of wound

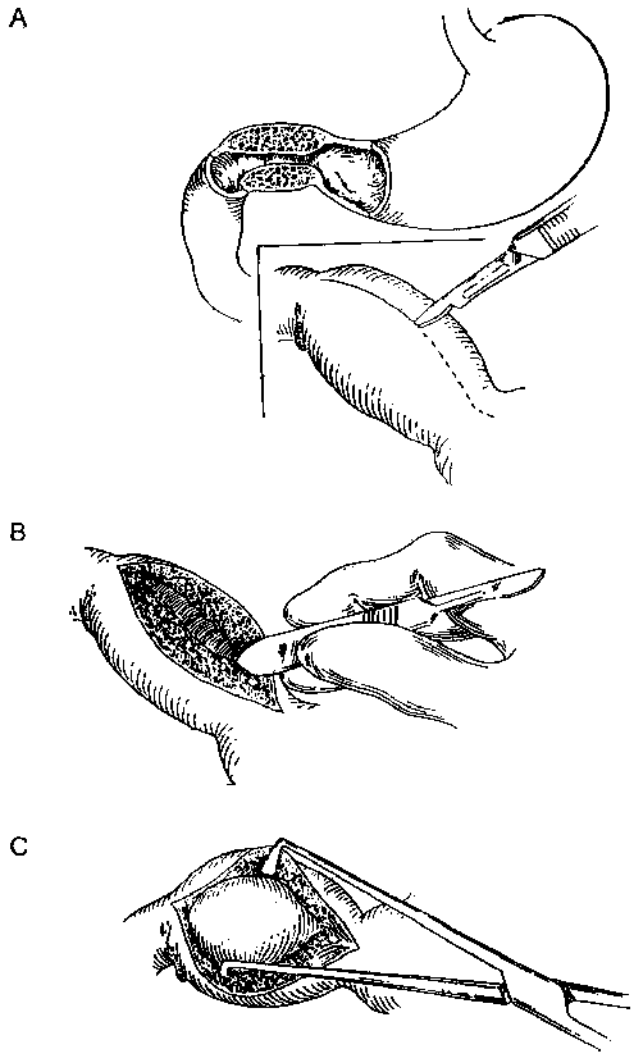


FIGURE 1 The Ramstedt extramucosal pyloromyotomy, the standard operative technique. (A) Cross-section of the pylorus, with inset showing the incision of the serosa on the anterior wall from just proximal to the pyloric vein to the antrum, just proximal to the area of hypertrophied muscle. (B) The myotomy is performed using the back of a scalpel handle to split the hypertrophied muscle bluntly down to the submucosa. (C) After exposure of the submucosa, the overlying muscle fibers are spread relatively widely, allowing the submucosa to herniate or bulge out. Reproduced with permission of the publisher from Ziegler, M. M. *et al.* "Operative Pediatric Surgery," Ch. 52. McGraw-Hill.

complications. Additionally, this incision is contraindicated in the presence of an umbilical remnant, a "wet" umbilicus, or periumbilical erythema. Laparoscopic pyloromyotomy has been gaining popularity since its first description by Alain and colleagues in 1991. This technique may have the advantage of improved appearance, but it has the disadvantage of longer operative times and a variable learning curve. No significant difference between the time the infant can resume full feedings or the length of hospital stay has been shown. A recent retrospective study found that outcomes between the open and laparoscopic techniques were similar, but the laparoscopic approach incurred a greater expense and decreased general surgery resident operative experience. Last, an additional technique, pyloric traumamyoplasty (either open or laparoscopic), has been introduced by various groups; this involves the used of a Babcock clamp to grasp and pinch the hypertrophied muscle, creating two lateral slits on the superior and inferior edges. Results with this technique have been shown to be similar to results with the traditional Ramstedt procedure, but experience to date has been limited.

Nonoperative management has not gained general acceptance in North America but has been practiced in some European countries. Infants can be managed with frequent small feedings or even temporary total parenteral nutrition, but this requires a prolonged hospital stay. Successful endoscopic balloon dilatation for pyloric stenosis has been reported in Japan, being used selectively in patients who have undergone previous extensive abdominal operative procedures. Botulinum toxin A has been attempted without success, whereas others have successfully used intravenous and oral atropine sulfate.

## POSTOPERATIVE MANAGEMENT

Most infants can be fed within 6 hours postoperatively. Many feeding regimens have been used, but most generally start with a small volume of sugar water, advancing volume and osmolarity every 2–3 hours until the child is taking formula or milk without significant vomiting. Data have shown that either a standardized feeding regimen or a more rapid, *ad libitum* feeding schedule will lead to earlier discharge, and the amount of vomiting with either technique is similar.

## OUTCOMES AND COMPLICATIONS

Mortality after pyloromyotomy has been extremely low, with reported rates of less than 0.5%. With appropriate management of fluids and electrolytes preoperatively and intraoperative management by a pediatric surgeon, most infants can be discharged from the hospital within 1–2 days. Similarly, morbidity is low; the major complications include wound infection or dehiscence, mucosal perforation, and inadequate pyloromyotomy. The incidence of wound infections has been variably reported from 1 to 5%. The reported rates of duodenal perforation range from 1 to 30% but generally remain in the 1–3% range in pediatric surgery centers. Although

many (30–90%) infants will have some degree of postoperative emesis, this usually resolves spontaneously within the first week. If prolonged emesis occurs, the possibilities of an unrecognized perforation, gastroesophageal reflux, or an incomplete myotomy should be considered. Contrast studies are of little value other than to diagnose a leak, because the radiologic and ultrasonographic appearances of the hypertrophied pylorus before and after pyloromyotomy are similar, and such an appearance may persist for many weeks to months. Therefore, the decision to reoperate for presumed incomplete myotomy is typically delayed for at least 2–3 weeks postoperatively.

Infrequent long-term effects of pyloromyotomy have been reported. One group evaluated the presence of gastrointestinal symptoms, gastric emptying, and pyloric measurements in adults after and without pyloromyotomy and found no differences. A second group found higher pyloric tone and force of gastric contraction, but no difference in clinically relevant gastric emptying in the same two treatment groups.

## SUMMARY

Pyloric stenosis is the most frequent cause of gastric outlet obstruction in children. Currently, the cause has not been definitively elucidated and appears to be multifactorial, although considerable basic science investigations are ongoing. The cardinal features of pyloric stenosis include nonbilious projectile vomiting, visible peristaltic waves in the left upper abdomen, a palpable olive (enlarged pylorus), and an associated hypochloremic, hypokalemic metabolic alkalosis. Diagnosis is made by history and physical examination alone or in combination with ultrasonography or gastrointestinal contrast studies. The Ramstedt extramucosal pyloromyotomy has long been the classic surgical approach to pyloric stenosis, although laparoscopic pyloromyotomy and traumamyoplasty are new additions to the operative armamentarium. Mortality and morbidity after pyloromyotomy have been extremely low and long-term sequelae of the procedure have not been reported.

## See Also the Following Articles

**Gastric Outlet Obstruction • Gastroesophageal Reflux Disease (GERD) and Congenital Esophageal Obstructive Lesions, Pediatric • Pyloroplasty • Pylorus • Webs**

## Further Reading


Campbell, B. T., McLean, K., Barnhart, D. C., Drongowski, R. A., and Hirschl, R. B. (2002). A comparison of laparoscopic and open pyloromyotomy at a teaching hospital. *J. Pediatr. Surg.* **37**, 1068–1071.

Dillon, P. W., and Cilley, R. E. (2000). Lesions of the stomach. *In* "Pediatric Surgery" (K. W. Asheraft, J. P. Murphy, R. J. Sharp, D. L. Sigalet, and C. L. Snyder, eds.), 3rd Ed., pp. 391–405. W. B. Saunders, Philadelphia.

Leinwand, M. J., Shaul, D. B., and Anderson, K. D. (2000). A standardized feeding regimen for hypertrophic pyloric stenosis decreases length of hospitalization and hospital costs. *J. Pediatr. Surg.* **35**, 1063–1065.

Letton, R. W. (2001). Pyloric stenosis. *Pediatr. Ann.* **30**, 745–750.

Lobe, T. E. (1995). Pyloromotomy. *In* "Rob & Smith's Operative Surgery, Pediatric Surgery" (L. Spitz and A. G. Coran, eds.), 5th Ed., pp. 320–327. Chapman & Hall, London.

Magnuson, D. K., and Schwartz, M. Z. (1997). Stomach and duodenum. *In* "Surgery of Infants and Children" (K. T. Oldham, P. M. Colombani, and R. P. Foglia, eds.), pp. 1133–1162. Lippincott-Raven, Philadelphia.

Poon, T. C., Zhang, A., Cartmill, T., and Cass, D. T. (1996). Changing patterns of diagnosis and treatment of infantile hypertrophic pyloric stenosis: A clinical audit of 303 patients. *J. Pediatr. Surg.* **31**, 1611–1615.

Schwartz, M. Z. (1998). Hypertrophic pyloric stenosis. *In* "Pediatric Surgery" (J. A. O'Neill, M. I. Rowe, J. L. Grosfeld, E. W. Fonkalsrud, and A. G. Coran, eds.), 5th Ed., Vol. 2, pp. 1111–1116. Mosby-Year Book, Inc., St. Louis.

Sun, W. M., Doran, S. M., Jones, K. L., Davidson, G., Dent, J., and Horowitz, M. (2000). Long-term effects of pyloromyotomy on pyloric motility and gastric emptying in humans. *Am. J. Gastroenterol.* **95**, 92–100.

Teele, R. L., and Smith, E. H. (1977). Ultrasound in the diagnosis of idiopathic hypertrophic pyloric stenosis. *N. Engl. J. Med.* **296**, 1149–1150.

# Pyloroplasty

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pyloroplasty Surgical procedure that incises and divides the normal pyloric muscle, destroying it as a sphincter, and then reconstructs the pyloric channel to facilitate gastric emptying.

vagotomy Surgical procedure in which the vagus nerves are cut, to reduce innervation of the stomach.

**Pyloroplasty is typically performed in conjunction with a truncal or selective vagotomy. Vagal denervation of the stomach is used to decrease gastric acid production in various acid-peptic disorders, but also results in failure of the antral–pyloric pump mechanism and markedly delays gastric emptying. Originally described in the late nineteenth century for use in the treatment of gastric outlet obstruction, pyloroplasty did not become a common procedure until vagotomy became the main treatment of peptic ulcer disease in the 1940s.**

## PHYSIOLOGY

The physiologic role of the normal pylorus remains controversial. Although it is thought to provide resistance to gastric emptying, to allow for complete mixing of gastric contents by the antral–pyloric pump, pyloroplasty (or pylorectomy) in dogs with normal gastric innervation causes little change in gastric emptying. After pyloroplasty alone, the gastric antrum can fulfill many of the functions of a normal pylorus. However, after vagotomy of the gastric antrum, the pylorus provides sufficient resistance to gastric emptying to cause markedly delayed gastric emptying of solids in more than one-third of patients. After vagotomy and pyloroplasty, the loss of proximal gastric receptive relaxation results in more rapid emptying of liquids despite a loss of antral pump function, presumably because of loss of gastric capacitance and loss of pyloric resistance to gastric emptying secondary to pyloroplasty.

## SURGICAL TECHNIQUE AND INDICATIONS FOR PROCEDURE

There are two different techniques for performing a pyloroplasty, the Heineke–Mikulicz/Weinberg variant and the Finney variant. A third procedure, Jaboulay pyloroplasty, is really a gastroduodenostomy without division of the pyloric ring and is therefore not technically a pyloroplasty. In the Heineke–Mikulicz/Weinberg variant, a longitudinal incision is made from the distal gastric antrum across the pylorus onto the first portion of the duodenum. This incision is then closed in a transverse fashion in either one or two layers of sutures, creating a wide gastric outlet (Fig. 1A). The advantage of this procedure is ease of performance. In the Finney variant, the duodenum is first mobilized and then approximated in a side-to-side fashion to the greater curvature of the stomach. A long incision is then made from the gastric antrum across the pylorus onto the duodenum. A side-to-side anastomosis is then constructed in two layers between the stomach and duodenum (Fig. 1B). The advantage of this procedure is that it produces a very large gastric outlet. However, significant scarring of the duodenum can make performance of a Finney pyloroplasty impossible. The main indication for a pyloroplasty is to facilitate gastric emptying after vagotomy. Historically, the most common use of pyloroplasty was in combination with truncal vagotomy in operations for peptic ulcer disease. With the marked decrease in elective surgery for peptic ulcer disease, the main modern use of pyloroplasty is in treating bleeding duodenal ulcers, to provide access to the ulcer and the gastroduodenal artery. It is now also commonly a component of reconstruction procedures following esophageal resection when the stomach is used as an esophageal conduit, in order to prevent gastric stasis in the intrathoracic stomach.

## COMPLICATIONS

The major complications associated with pyloroplasty and vagotomy include dumping syndrome, which is seen in up to 20% of patients. Postvagotomy diarrhea is seen in approximately 10% of patients after the procedure. Early satiety and epigastric fullness are seen in many patients in the early postoperative period, but usually resolve spontaneously over time. Bile reflux and bilious vomiting are seen in 2–5% of patients after pyloroplasty. In one study with long-term followup

 

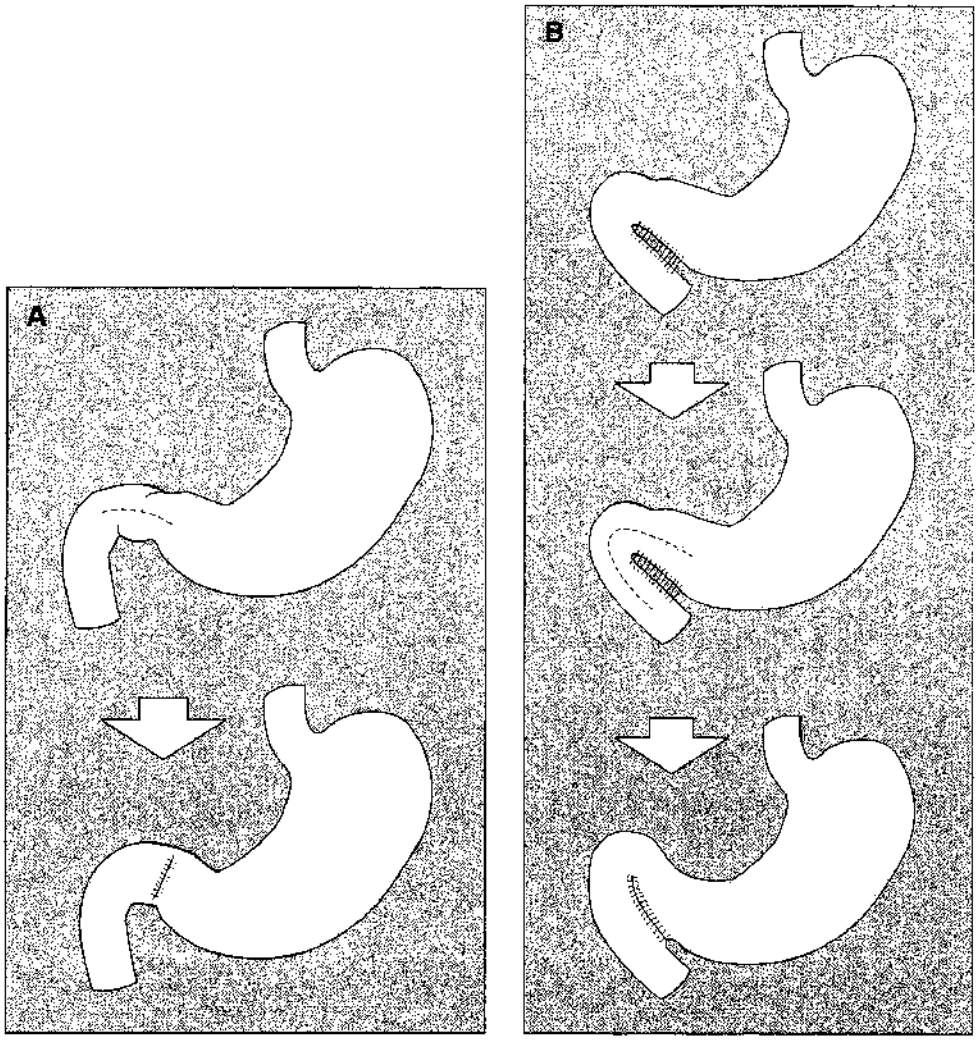


**FIGURE 1** (A) In a Heineke–Mikulicz pyloroplasty, a horizontal incision is made across the pylorus and then is closed vertically, to widen the pyloric orifice. (B) In a Finney pyloroplasty, a back row of seromuscular sutures is first placed to approximate the duodenum and the greater curvature of the antrum. A U-shaped incision is then made from the antrum across the pylorus onto the duodenum. This is then closed in two layers, to construct a side-to-side gastroduodenal anastomosis. Illustrations by Jim Hardy, VA North Texas Health Center.

after vagotomy and pyloroplasty, 40% of patients experienced some gastrointestinal disturbance, and 6% of patients experienced severe disturbances.

## See Also the Following Articles

**Dumping Syndrome • Gastric Outlet Obstruction • Gastric Surgery • Pylorus**

## Further Reading

Dayton, M. (2002). Vagotomy and drainage (2002). *In* "Shackelford's Surgery of the Alimentary Tract" (D. Dempsey, ed.), 5th Ed., Vol. 2, pp. 117–130. W. B. Saunders, Philadelphia.

Richter, H. (1994). Physiologic consequences of vagotomy and gastric resection. *Gastroenterol. Clin. North Am.* 23(2), 193–213.

Skellenger, M., and Jordan, P. (1983). Complications of vagotomy and pyloroplasty. *Surg. Clin. North Am.* 63(6), 1167–1178.

# Pylorus

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**bile reflux** Movement of bile from the small intestine (duodenum) into the stomach.

**dumping syndrome** Abnormally rapid emptying of stomach contents into the small intestine, associated with symptoms of dizziness, rapid heart rate, sweating, nausea, and diarrhea occurring mainly after a meal.

**pyloric stenosis** Narrowing of the pyloric (outlet) region of the stomach.

**pyloric tone** Variable level of ongoing contraction of the musculature in the pyloric region of the stomach.

**pyloroplasty** A surgical procedure that enlarges the opening separating the stomach from the small intestine.

**Pylorus means gatekeeper in Greek. The term aptly reflects the fact that the pylorus controls the resistance to flow across the narrow gastric outlet. The diameter of the pylorus is set by the baseline tension of the pyloric muscle (pyloric tone). Forceful pyloric closure is part of the terminal antral contraction that leads to retropulsion of gastric contents. The pyloric sphincter is a complex muscular structure that is enforced by dense connective tissue.**

## ANATOMY

The pyloric segment extends from the proximal pyloric muscle loop (PPL) to the distal pyloric muscle loop (DPL) (see Fig. 1). The PPL is a broad band of circular muscle that fans out from the lesser curvature close to the duodenal bulb and reaches the greater curvature several centimeters upstream. The DPL is a thick bundle of circular muscle at the base of the duodenal bulb. Reinforced by collagen-rich connective tissue, this pyloric ring surrounds the narrow lumen of the pyloric orifice. PPL and DPL converge on the lesser curvature in a knot of connective tissue and fat, known as pyloric torus. On contraction, the torus wedges into the groove between the two muscle loops on the greater curvature. The pyloric canal refers to the lumen inside the contracted pyloric segment.

## PHYSIOLOGY AND INNERVATION

The pylorus differs from other gastrointestinal sphincters in that it does not occlude the lumen at rest. As gastric contractions reach the PPL, the entire pyloric segment closes in rapid sequence, the terminal antral contraction. Antral folds prolapse into the pylorus and form a mucosal plug, which reduces the pyloric lumen to a star-like slit. Simultaneously, the pylorus shortens and moves orad and toward the left. As the contraction passes, the pyloric segment flares open from its proximal end.

Pyloric activity is controlled by enteric nerves in the myenteric plexus. Tonic inhibitory nervous input maintains the pylorus in a relaxed state at rest. Inhibitory nerves release nitric oxide and/or vasoactive intestinal peptide. Nitridergic inhibition of the pylorus occurs with vagal and antral stimulation. Excitatory cholinergic and enkephalinergic neurons stimulate pyloric muscle tone and contractions.

Enteric neurons synapse with sympathetic neurons from the celiac plexus and parasympathetic (vagal) neurons via the nerve of Latarjet. The pyloric musculature contains fewer interstitial cells of Cajal than the gastric and duodenal musculature.

## FUNCTION

Pyloric activity adapts to the properties of the luminal contents. A widely patent pylorus (diameter of approximately 1 cm in humans) allows for rapid outflow of isotonic solutions. Acid increases pyloric tone through cholinergic stimulation and slows flow. Fat triggers intermittent pyloric contractions in the absence of antral or duodenal activity (isolated pyloric contractions). Contractions of proximal stomach and antrum drive boluses of liquids and small particles through the pylorus. Larger particles and fat are trapped by the terminal antral contraction before reaching the pyloric orifice and are dispersed by a powerful retrograde jet. The separation of liquid and solid phases at the gastric outlet is known as sieving and occurs in part through decanting. Phasic contractions of pylorus and antrum generate the shear forces that break down particles and mix particles, fat droplets, and secretions to the slurry known as gastric chyme.

 

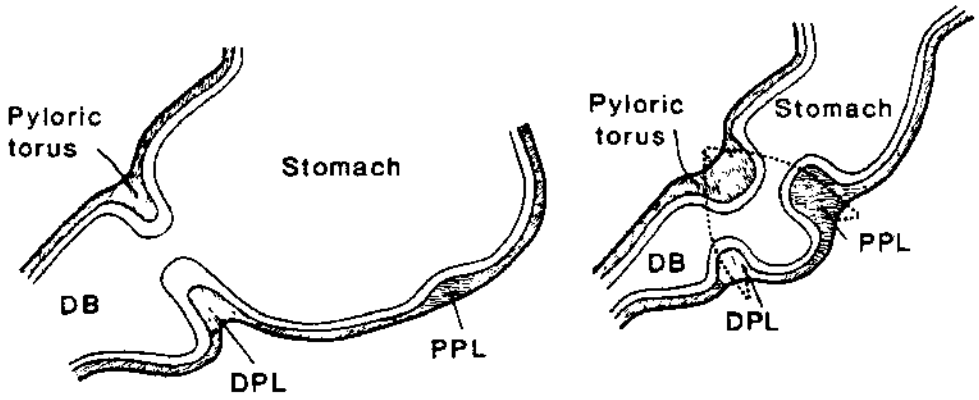


**FIGURE 1** Scheme of the relaxed (left) and contracted (right) pylorus. DB, duodenal bulb; DPL, distal pyloric loop; PPL, proximal pyloric loop. (Right) The contraction of the pyloric muscle loops has led to closure of the pyloric canal. Reprinted from Keet, A.D., Jr. (1957). The prepyloric contractions in the normal stomach. *Acta Radiol.* 48, 413–424, with kind permission of the author and editor of *Acta Radiologica*.

## ABNORMAL FUNCTION

Pyloric function may be affected by operative intervention (gastric resection, pyloroplasty), by denervation (vagotomy, diabetic autonomic neuropathy), by muscular hypertrophy, or by mucosal inflammation (peptic ulcer disease). Pyloric incompetence leads to precipitous gastric emptying or dumping, particularly of fluids. Diarrhea and maldigestion may result. Pyloric stenosis leads to gastric retention, vomiting, and weight loss.

### Infantile Hypertrophic Pyloric Stenosis

Infantile hypertrophic pyloric stenosis refers to gastric outlet obstruction from muscular hypertrophy. It affects 1 of 150 males and 1 of 750 females at birth. A deficiency of nitric oxide-containing neurons is invoked.

### Peptic Disease

Peptic disease can cause pyloric deformation. The disruption of the torus and DPL leads to a short, wide, and incompetent pylorus. A "keyhole" deformity of the pylorus and foreshortening of the duodenal bulb may be seen. Scars involving the PPL produce an antral web and a long stenotic pylorus.

### Denervation

Vagotomy may result in a functional pyloric stenosis (pylorospasm). An autovagotomy is considered to be responsible for disrupted gastroduodenal motor activity and pylorospasm in autonomic neuropathy, particularly in diabetes mellitus.

### See Also the Following Articles

Dumping Syndrome • Electrogastrography • Gastric Motility • Pyloric Stenosis • Sphincters

### Further Reading

Allescher, H.-D., and Daniel, E.-E. (1994). Role of NO in pyloric, antral and duodenal motility and its interaction with other inhibitory mediators. *Digest. Dis. Sci.* 39, 73S–75S.

Biancani, P., Zabinski, M.-P., Kerstein, M.-D., and Behar, J. (1979). Mechanical characteristics of the cat pylorus. *Gastroenterology* 77, 301–309.

Ehrlein, H.-J. (1988). Motility of the pyloric sphincter studied by the inductograph method in conscious dogs. *Am. J. Physiol.* 254, G650–G657.

Lu, C.-C., and Schulze-Delrieu, K. (1990). Pyloric deformation from peptic disease—Radiographic evidence for incompetence rather than obstruction. *Digest. Dis. Sci.* 35, 1459–1467.

Mearin, F., Camilleri, M., and Malagelada, J.-R. (1986). Pyloric dysfunction in diabetics with recurrent nausea and vomiting. *Gastroenterology* 90, 1919–1925.

Torgensen, J. (1942). The muscular build and movements of the stomach and duodenal bulb. *Acta Radiol.* 45, 1–191.

# Radiology, Interventional

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Interventional radiology (IR) is a subspecialty of radiology, which is based on the use of imaging techniques for diagnostic purposes and to guide minimally invasive therapeutic procedures. For example, in a patient with bleeding into the gastrointestinal tract, a small catheter is inserted percutaneously into the femoral artery in the groin. The catheter is then manipulated up the aorta and selectively into a mesenteric artery, using fluoroscopic guidance. An X-ray contrast agent is injected through the catheter and radiographs are taken. These identify and locate a bleeding site within the bowel, providing an excellent diagnostic test. Then, an embolic agent, such as a metallic coil, can be injected through the same catheter to block the bleeding artery and provide the definitive treatment to stop the bleeding. These image-guided minimally invasive techniques are not only used intravascularly, but are valuable in many other gastrointestinal applications, such as in the lumen of the alimentary tract, percutaneously into the liver, biliary tract, and other viscera, and for the drainage of abscesses or fluid collections. The instruments employed are typically needles, wires, catheters, balloons, snares, collapsible baskets, emboli, and other small-caliber devices. Guidance may be provided by X-ray image-intensified fluoroscopy, computed tomography, ultrasonography, or less commonly, magnetic resonance imaging. In most cases, the procedures are accomplished under local anesthesia with moderate sedation, eliminating the need for general anesthesia, which is often needed for conventional surgical interventions. Recovery time is typically much shorter than for surgery and many procedures can be performed on an outpatient basis. No surgical incisions are needed. The use of IR in the gastrointestinal tract as it pertains to the different parts of the gastrointestinal tract will be described.

## ALIMENTARY CANAL

### Feeding Tube Manipulation

Patients often are unable to eat or to feed themselves because of impaired consciousness or other temporary problems. A simple temporary solution is to pass a small tube into the nose, through the esophagus, and into the stomach.

This can be carried out by a nurse at the bedside. Some patients do not empty their stomachs well, so that the liquid nutrients injected down the tube, called a feeding tube or nasogastric tube, accumulate in the stomach and may cause reflux into the lungs and aspiration pneumonia. Using fluoroscopic guidance and guide-wire and catheter techniques, the interventional radiologist can maneuver these tubes deep into the third part of the duodenum. This stops reflux and delivers the nutrients to the jejunum, where they can be absorbed.

### Percutaneous Gastrostomy

Nasogastric tubes are not suitable for long-term use because they are uncomfortable for patients and may become dislodged. Long-term tube feeding to the stomach or the jejunum can best be achieved by placing the tube percutaneously through the anterior abdominal wall directly into the lumen of the stomach. This can be done during open surgery, by laparoscopic techniques, by combined gastric endoscopy and surgery, and most simply by direct puncture under fluoroscopic guidance by the interventional radiologist. The interventional radiology technique is to inflate and distend the stomach with air injected down a nasogastric tube. The stomach pushes up against the anterior abdominal wall and displaces all other structures. The entry site is just below the left costal edge in line with the nipple. The procedure is performed using local anesthesia and moderate sedation. A needle is passed percutaneously into the distended air-filled stomach, which is easily seen fluoroscopically. T-fasteners are deployed through three separate needle punctures and are used to fix the stomach to the anterior abdominal wall. A fourth puncture is used to place a stiff guide wire into the stomach. Serially enlarging dilators are used over the wire to enlarge the tract. Finally, a 14-French self-retaining catheter is passed over the wire and provides access to feed the stomach.

 

### Diagnosis of Bowel Ischemia

The arterial blood supply to the bowel comes from three main arteries arising from the aorta. These are the celiac trunk, the superior mesenteric artery, and the inferior mesenteric artery. An additional arterial collateral supply can be developed via branches of the internal iliac arteries. Placement of a catheter in the aorta allows the injection of contrast agent and the filming of an angiogram to show any blockage of the arteries or veins that may cause the bowel to be ischemic or have an impaired blood supply. With rapid progress in noncatheter angiography techniques such as computed tomography (CT) or magnetic resonance imaging (MRI), catheter angiography may be needed infrequently and will be largely supplanted by the noninvasive techniques. It is important to demonstrate the site of acute arterial occlusion at an early stage so that treatment can be instituted before lack of blood causes irreversible ischemic necrosis and perforation of the bowel.

### Diagnosis and Treatment of Intestinal Bleeding

Catheter angiography is an important and accurate method of demonstrating the actual intestinal bleeding site. An angiogram is performed, opacifying the arterial tree supplying the bowel. Bleeding is demonstrated by the leakage of contrast from the lumen of the artery, causing a persistent stain or collection of extravascular contrast agent. Once the site of active bleeding is demonstrated, it is possible in many cases to pass a small catheter selectively down the bleeding artery to the point of the bleeding. The artery is then sealed off at this point, by the trans-catheter injection of an embolic agent such as a metal coil or polylvinyl alcohol particles. This treatment is rapid and effective and eliminates the need for conventional surgical operative treatment. The interventional treatment of variceal bleeding from portal hypertension is described below under transjugular intrahepatic portosystemic shunt (TIPS). X-ray fluoroscopy provides the visualization necessary to guide these procedures.

### Stricture Dilation

Strictures at each end of the gut can be traversed by catheter and guide-wire techniques allowing for the coaxial passage of dilating balloons or, in addition, expandable metallic stents. Malignant and benign strictures of the esophagus, duodenum, and recto-sigmoid colon have been successfully treated and stricture dilations have been useful as palliation in terminal malignancy or as preparation for surgery on the colon.

## LIVER

### Tumor Ablation

Tumors or metastatic masses in the liver that cannot be surgically excised can be completely or partially destroyed by percutaneous alcohol injection directly into the tumor, by percutaneous placement of a radiofrequency probe into the tumor, which delivers heat energy to destroy the tumor mass, or, alternatively, by destroying the tumor via freezing, using a cryoprobe placed into the tumor mass. A different approach is selective infusion of chemo-embolic agents through an arterial catheter. This technique delivers high concentrations of agents specifically targeted at the tumor cells and is less toxic than intravenous administration of these agents. Blocking the feeding artery with emboli reduces the oxygenation to the tumor cells, making them more vulnerable to the chemotherapeutic drugs. All these procedures are dependent on image guidance techniques such as fluoroscopy, ultrasound, CT, MRI, or a combination of two modalities. The effectiveness of these procedures varies greatly from occasional complete cure to minimal palliation. The results depend on the size of the mass, the number of masses, the location of the masses, and the etiology of the masses.

### Diagnosis and Treatment of Bleeding

Bleeding can occur in the liver due to trauma, iatrogenic injury such as biopsy, or tumors. Angiography can be used to identify the site of bleeding and then the bleeding can frequently be stopped using selective trans-catheter embolization.

### Percutaneous Cholecystostomy

The gallbladder can be drained percutaneously in patients who have inflammation of the gallbladder (cholecystitis), who have an obstruction of the cystic duct draining the gallbladder, or who have stones in the gallbladder. These patients would usually undergo surgical removal of their gallbladders, but they may require percutaneous drainage as a temporary measure until they are well enough to have surgery. The drainage catheter is placed into the gallbladder via a percutaneous needle puncture and coaxial guide-wire technique using ultrasound guidance.

## Percutaneous Transhepatic Cholangiography

In a similar manner, a thin 22-gauge needle can be passed percutaneously into a bile duct. Contrast material is injected through the needle, thus opacifying the bile ducts. X-ray films can then be taken showing the anatomy and any pathological changes of the bile ducts. The procedure is performed under fluoroscopic guidance and in a number of cases ultrasound can also be used to assist in duct puncture, especially on the left side of the liver. Percutaneous transhepatic cholangiography (PTC) is of particular value when retrograde endoscopic cholangiography is not possible. PTC is the first step in percutaneous transhepatic biliary drainage, described in the next section.

## Percutaneous Transhepatic Biliary Drainage

Once a bile duct has been punctured, as described above, a guide wire can be passed through the needle into the lumen of the punctured bile duct. The needle is removed and a catheter can be passed over the retained guide wire into the duct, establishing access from the skin to the biliary tree. This percutaneous, skin-to-duct tract provides a route for drainage of a blocked system, access for balloon dilation of strictures, stone removal, or endolumenal biopsy. Expandable metallic stents can be placed via this route to keep narrowed ducts open. These techniques have found wide application in both the treatment of benign disease and the palliation of malignant disease.

## Transjugular Intrahepatic Portosystemic Shunt

One of the most dramatic procedures highlighting the scope of interventional radiology is the TIPS procedure, in which a shunt is created by making a tract through the substance of the liver to connect the portal vein directly to the hepatic vein (Fig. 1). TIPS is used as a treatment for the serious condition of high pressure in the portal vein (portal hypertension). The consequences of portal hypertension are life-threatening gastrointestinal bleeding and ascites. A long needle is passed via a percutaneous puncture of the internal jugular vein in the neck, down through the superior vena cava and the right atrium, and into the right hepatic vein. The needle

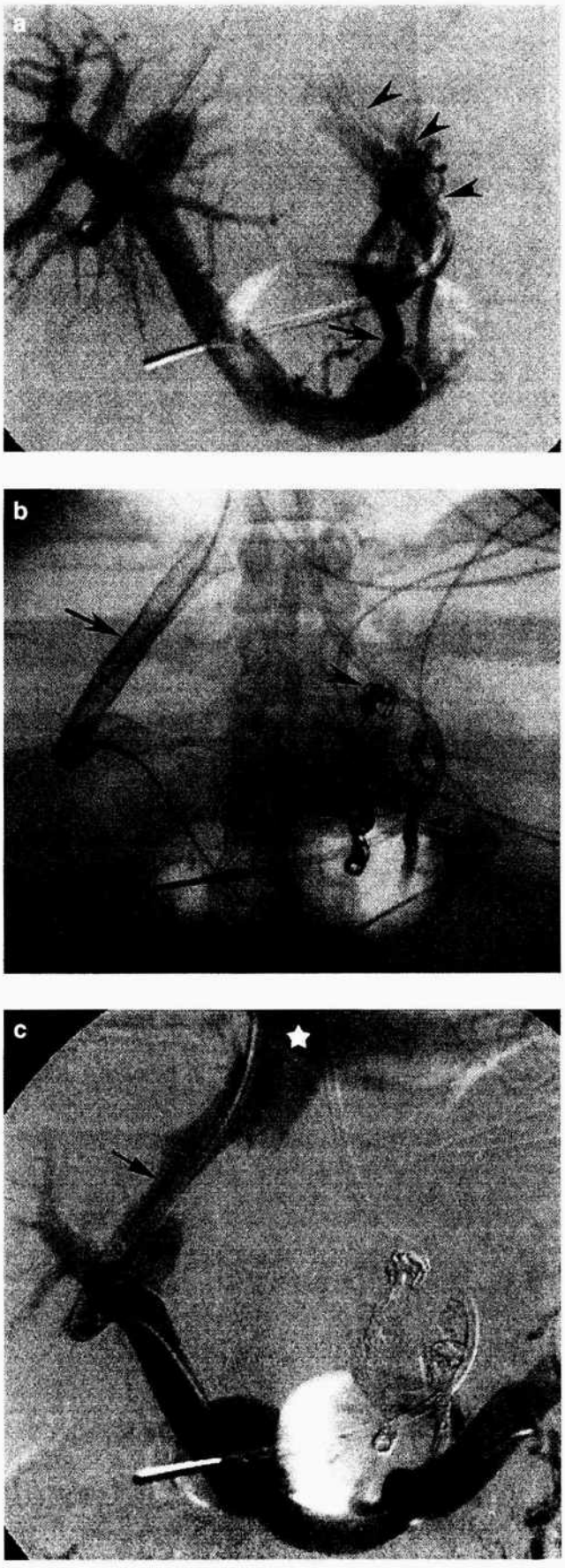


FIGURE 1 (a) Transjugular portal venogram showing abnormally large coronary vein (arrow) and varices (arrowheads). (b) The TIPS has been constructed and the metal stents are easily seen (arrow). Metal coils have been used to block the varices (arrowheads). (c) Completion venogram shows that blood flows from the portal vein through the TIPS (arrow) to the right atrium (star). The varices no longer fill with blood.

is then passed through the substance of the liver to puncture the right portal vein within the liver. This passage is then dilated with a balloon catheter and it is kept open by means of an expandable metallic sent. Blood is shunted through this newly created tract, bypassing the diseased liver and flowing directly from the portal system to the hepatic vein and then to the inferior vena cava. The portal system is decompressed, which stops portal bleeding and allows ascites to resolve.

## ABSCESS DRAINAGE

Imaging techniques such as ultrasound, CT, and MRI provide an excellent demonstration of any fluid accumulations or abscesses within a patient's body. In most cases, a needle can be inserted percutaneously under local anesthesia into the collection, using ultrasound, CT, or possibly MRI guidance. Then, via the needle lumen, a guide wire is inserted and the needle is exchanged for serially enlarging dilators and finally a self-retaining catheter to provide drainage. Occasionally it is sufficient to just aspirate the contents of the collection via the needle. Percutaneous abscess drainage is in very frequent use and has greatly improved and simplified the scope of care of patients with primary abscesses and especially of patients with postoperative abscesses.

## BIOPSY

The same image-guided techniques allow the needle biopsy of suspicious lumps in all parts of the body. Often, aspirating some tissue cells through a thin needle is enough to allow the cytologist to make a diagnosis. In other instances, a large-caliber needle is used to provide a core biopsy for full histological examination. Percutaneous biopsy is safe, simple, and effective and is widely used.

## See Also the Following Articles

**Alimentary Tract, MRI of the • Cholecystectomy • Computed Tomography (CT) • Gastrostomy • Lower Gastrointestinal Bleeding and Severe Hematochezia • Magentic Resonance Imaging (MRI) • Percutaneous Transhepatic Cholangiography (PTC) • Upper Gastrointestinal Bleeding**

## Further Reading

Backal, C. W. (2002). "Vascular and Interventional Radiology: Principles and Practice." Thieme, Stuttgart, Germany.

LaBerge, J. M., Gordon, R. L., Kerlan, R. K., and Wilson, M. W. (2000). "Interventional Radiology Essentials." Lippincott Williams & Wilkins, Philadelphia, PA.

Valji, K. (1999). "Vascular and Interventional Radiology." W. B. Saunders, Philadelphia, PA.

# Rectal Ulcers

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**erosion** A partial-thickness mucosal defect.
**neoplasia** The pathological process that results in the formation and growth of a tumor.
**prolapse** The descent of a body part from its usual anatomical position.
**tenesmus** A physical symptom described as urgent, painful, and ineffective straining at stool.
**ulcer** A full-thickness mucosal defect.

**Rectal ulcers are full-thickness defects of the rectal mucosa. They typically present clinically with rectal bleeding or pain. As in other portions of the colon, various pathologic processes and injurious agents can lead to rectal mucosal injury and resultant pathologic changes ranging from focal erythema or erosion to ulceration. The injury may be localized to the rectum or the rectum may be affected by disease processes that also affect other portions of the colon. The diagnosis of rectal ulcers is based on a typical clinical presentation combined with characteristic endoscopic and histologic findings.**

## INTRODUCTION

Rectal mucosal ulceration represents a nonspecific effect of mucosal injury. The injury may be confined to the rectum or it may be diffuse or multifocal, also affecting other portions of the gastrointestinal tract. The type of injury varies, but common causes of rectal mucosal injury include ischemia, physical trauma, and infection. The degree of mucosal injury depends on the timing, type, and severity of the injury, and the resultant pathologic changes range from mild mucosal erythema to erosion and, ultimately, ulceration. This article focuses on the clinicopathologic features of common diseases in which rectal ulceration can occur. These entities are divided into those processes that typically are limited to the rectum and those in which rectal involvement may occur as part of a more diffuse colonic disease.

## ULCERS UNIQUE TO THE RECTUM

### Mucosal Prolapse Syndromes

The mucosal prolapse syndromes [solitary rectal ulcer syndrome (SRUS), rectal prolapse, proctitis cystica profunda (PCP), and inflammatory cloacogenic polyp] are a group of entities characterized by rectal mucosal injury related to mucosal prolapse. The mucosal prolapse syndromes often coexist and exhibit overlapping clinical, endoscopic, and histologic features. The endoscopic and histologic features depend on the frequency, location, and duration of prolapse and the underlying cause. All of these entities are united by a similar process of injury resulting in ulceration followed by mucosal regeneration, leading to the development of a polypoid lesion. The syndromes have been referred to by the various names listed above, depending on which histologic feature is most prominent.

Patients affected by mucosal prolapse typically present in the third or fourth decade with symptoms of anorectal disease. Patients may complain of rectal bleeding, diarrhea, anorectal pain, abdominal cramps, difficulty defecating (constipation, straining, rectal prolapse, or a sense of incomplete rectal emptying), or fecal incontinence. Endoscopic examination reveals ulcerated, polypoid, and/or indurated areas, most often located on the anterior or anterolateral wall. Ulcers, if present, often straddle a rectal fold and vary in size from a few millimeters to several centimeters in diameter. Ulcers are not always present, however, and some patients only have an erythematous area with or without polypoid projections.

#### *Solitary Rectal Ulcer Syndrome*

Solitary rectal ulcer syndrome is characterized by the presence of ulcers or polypoid inflammatory lesions in the rectum (Fig. 1). The descriptive name of this condition is misleading, however, as the lesions are frequently multiple and in almost half of the cases there is no ulceration. This entity affects both children and adults, mostly those between 20 and 40 years of age, and is more common in women. The most common symptom is rectal bleeding during defecation, followed by mucus discharge, anorectal or abdominal pain, and tenesmus. Most patients report having had symptoms for many years and many cases are initially misdiagnosed.

 

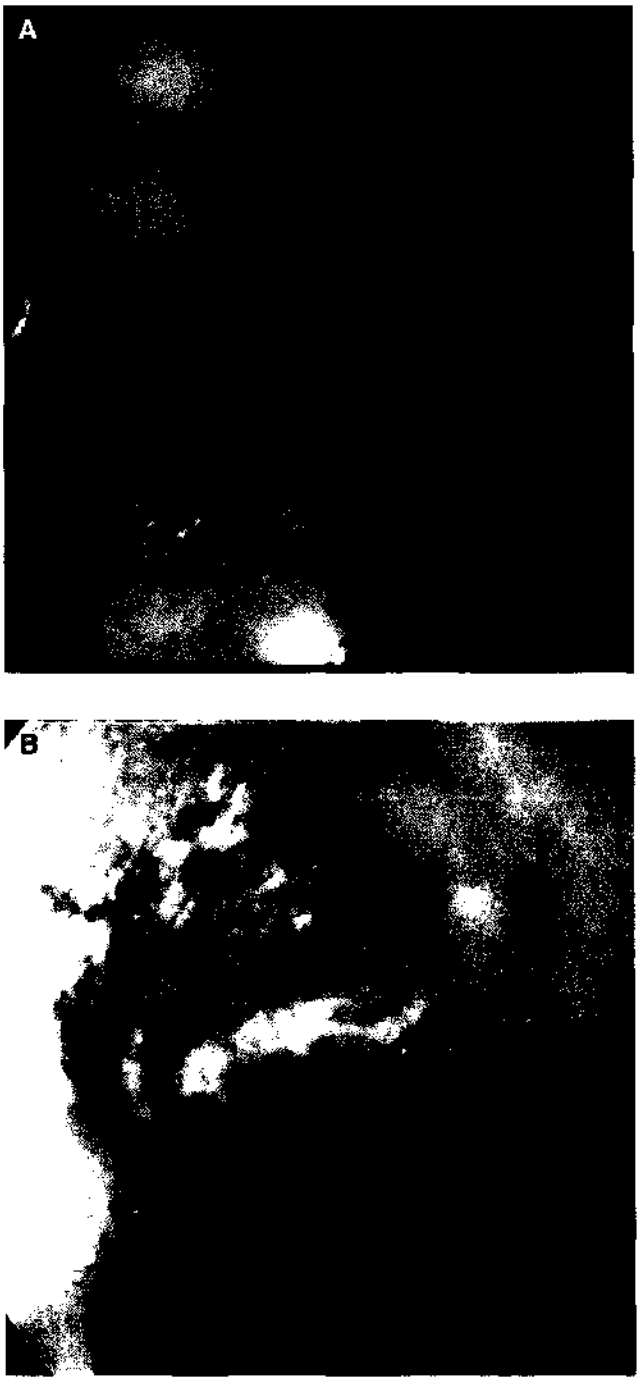


FIGURE 1 Endoscopic images of solitary rectal ulcer syndrome. (A) Typical case of solitary rectal ulcer syndrome, exhibiting polypoid projection of rectal mucosal but no ulceration. (B) Solitary rectal ulcer with ulceration overlying prolapsed rectal mucosa.

The pathogenesis of SRUS is related to abnormal colonic motility. Most patients with SRUS have abnormal contraction of the puborectalis muscle, increased external sphincter tone, increased intrarectal pressure during evacuation, and overt or occult prolapse of the rectal mucosa. The pathogenesis is related to inadequate relaxation of the internal anal sphincter or the overall rectal musculature, resulting in excessive straining during defecation. The combination of intermittent mucosal prolapse with vascular compromise and mechanical trauma to the mucosa results in mucosal erosions. With repeated episodes, there is progressive injury and mucosal regrowth, leading to the formation of a polyp.

The diagnosis of SRUS is based on symptoms in conjunction with the characteristic endoscopic and histologic findings. In some cases a cystic mass, polyp, or a sessile villous lesion may be seen. The lesions occur most frequently on the anterior or anterolateral rectal wall, but can be more extensive and may even be circumferential. Histologic sections often show features of mucosal hyperplasia, often exhibiting architectural distortion with serration of glandular lumens. There may be surface erosion or ulceration. There is often fibrosis or neovascularization of the lamina propria and thickening of the muscularis mucosae, with upward extension of smooth muscle fibers into the lamina propria.

The prognosis for SRUS varies. The lesions may regress, remain stable, or progress and become disabling. Although there is no definitive therapy for SRUS, symptoms may be reduced by conservative measures including dietary modifications, local agents to promote tissue regeneration, or biofeedback behavioral training to correct the abnormal defecation process. In severe cases, surgical treatment may be considered.

### *Rectal Prolapse*

Rectal prolapse is the descent of some or all of the layers of the rectal wall through the anal sphincter. Rectal prolapse occurs in infants, is uncommon in children and young adults, and increases in frequency after age 40. Patients with rectal prolapse often complain of straining or pain during defecation, fecal incontinence, mucus discharge, pruritus, rectal bleeding, a sense of obstruction of incomplete rectal evacuation, and perineal or intervaginal pressure. The presence of reddened, protruding rectal mucosa is characteristic of rectal prolapse or a palpable mass may be detected on digital rectal examination (Fig. 2). There may be surface erosion or ulceration. Because the lesions can have an endoscopic appearance and a clinical presentation similar to rectal cancer, histologic analysis is important for diagnosis. Histologic features are similar to those seen in SRUS.

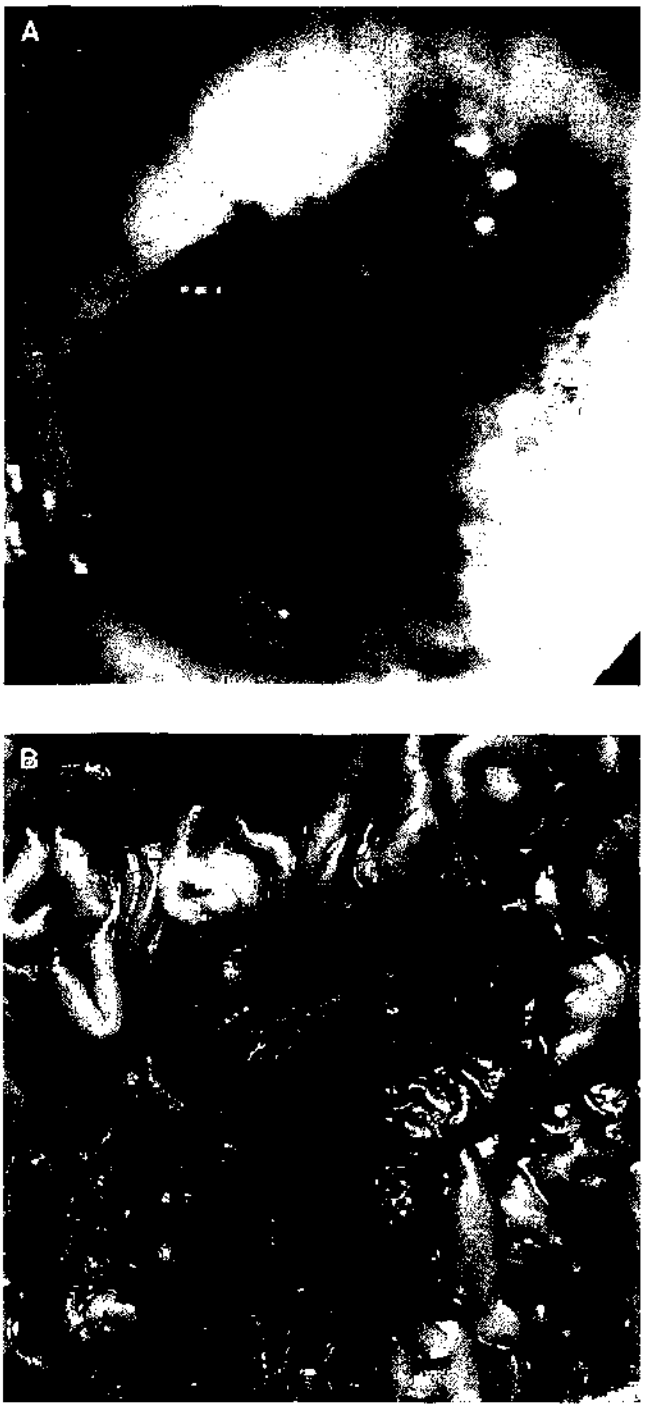


FIGURE 2 Endoscopic (A) and gross resection specimen (B) images of rectal mucosal prolapse. Clinically and endoscopically the lesion was suspected to represent rectal cancer. However, histologic analysis of the endoscopic biopsies and evaluation of the resection specimen confirmed the diagnosis of rectal mucosa prolapse.

### *Proctitis Cystica Profunda*

Proctitis cystica profunda is the deep displacement of rectal mucosa through the muscularis mucosae and into the submucosa or deeper parts of the intestinal wall. This entity represents regenerative changes following deep ulceration of the colon from any cause. Patients may complain of blood and mucus in stools, but PCP may not be symptomatic. PCP most commonly occurs as an isolated lesion in the late stages of SRUS but multiple small lesions may be seen in chronic inflammatory conditions such as inflammatory bowel disease. PCP is rarely observed in an otherwise apparently normal colon.

PCP may not be visible endoscopically, frequently presenting as an incidental histologic finding. When observed grossly, PCP may appear as a raised or polypoid lesion, as focal mucosal edema or erythema, or with obvious cysts from which thick mucus may exude when compressed. Histologic sections reveal cystically dilated colonic glands within the submucosa or deeper in the intestinal wall. The glandular epithelium is usually normal or hyperplastic, but may show regenerative features.

### *Inflammatory Cloacogenic Polyp*

Inflammatory cloacogenic polyp is a polypoid prolapse of the anorectal transitional zone mucosa. It typically presents in the fifth to seventh decades as a small, sessile polyp at the anorectal junction. It was originally defined by its surface lining of transitional-type epithelium, but this feature is now thought to represent a metaplastic change in SRUS. This inflammatory polyp has histologic features similar to those seen in mucosal prolapse and SRUS, including fibrosis and smooth muscle fibers extending into the lamina propria. These similarities suggest that prolapse may be important in the pathogenesis of these polyps and have led some authors to include this entity in the mucosal prolapse syndromes.

## Stercoral Ulcer

Stercoral ulcers are longitudinal mucosal tears or perforations that result from fecal impaction. They occur most frequently in the distal colon and rectum. Patients typically present with severe chronic constipation, pain, and rectal bleeding. The hard, impacted fecal material causes localized pressure, ischemia, and subsequent necrosis of the mucosal surface. The ulcers may be single or multiple and usually have sharply defined edges and there is congestion of the adjacent mucosa. Most lesions are confined to the submucosa, but deeper ulceration and perforation can occur. Biopsy may be obtained to exclude other inflammatory causes of ulceration or neoplasia. Histologic sections of the early lesions reveal ischemic injury with extensive necrosis and entrapped fecal material,

vascular congestion, and patchy hemorrhage. Chronic ulcers show reparative changes, fibrosis, and inflammation and may exhibit a granulomatous response to the fecal matter.

## RECTAL INVOLVEMENT IN DISEASES ALSO AFFECTING OTHER PORTIONS OF THE GASTROINTESTINAL TRACT

In addition to mucosal prolapse syndromes and stercoral ulcer, which typically affect the rectum, rectal involvement may also occur as part of a more diffuse colonic disease. Inflammatory bowel disease (Crohn's disease and ulcerative colitis) can present with localized rectal disease or with rectal involvement by more diffuse disease. Ischemic bowel disease can involve the rectum and may cause mucosal ulceration. Localized rectal ulcers can occur with the use of nonsteroidal anti-inflammatory drugs, especially when used as a suppository. Radiation injury to the rectum occurs when high doses of radiation are used to treat tumors arising in the pelvis. Ulceration is a common feature of many infectious processes. Those that typically affect the rectum include syphilis and herpes infections, both of which are spread by direct inoculation and cause ulceration.

## See Also the Following Articles

**Colitis Cystica Profunda and Solitary Rectal Ulcer Syndrome • Colitis, Ulcerative • Crohn's Disease • Solitary Rectal Ulcer Syndrome**

## Further Reading

Cooper, H. (1998). Benign epithelial polyps of the intestines. *In* "Pathology of the Gastrointestinal Tract" (S. Ming and H. Goldman, eds.), 2nd Ed., pp. 819–853. Williams & Wilkins, Baltimore, MD.

Fenoglio-Preiser, C., Noffsinger, A., Stemmermann, G., Lantz, P., Listrom, M., and Rilke, F. (eds.) (1999). "Gastrointestinal Pathology: An Atlas and Text." Lippincott-Raven, Philadelphia, PA.

Goldman, H. (1998). Other inflammatory disorders of the intestines. *In* "Pathology of the Gastrointestinal Tract" (S. Ming and H. Goldman, eds.), 2nd Ed., pp. 719–753. Williams & Wilkins, Baltimore, MD.

Levine, D. (1987). "Solitary" rectal ulcer syndrome: Are "solitary" rectal ulcer syndrome and "localized" colitis cystica profunda analogous syndromes caused by rectal prolapse? *Gastroenterol.* 92, 243–253.

Poon, K., Mills, S., Booth, I., and Murphy, S. (1997). Inflammatory cloacogenic polyp: An unrecognized cause of hematochezia and tenesmus in childhood. *J. Pediatr.* 130, 327–329.

Tendler, D., Aboudola, S., Zacks, J., O'Brien, M., and Kelly, C. (2002). Prolapsing mucosal polyps: An underrecognized form of colonic polyp: A clinicopathological study of 15 cases. *Am. J. Gastroenterol.* 97, 370–376.

Tsiaoussis, J., Chrysos, E., Glynos, M., Vassilakis, J., and Xynos, E. (1998). Pathophysiology and treatment of anterior rectal mucosal prolapse syndrome. *Br. J. Surg.* 85, 1699–1702.

# Rectum, Anatomy

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**mucosa** Surface epithelial layer.
**rectum** Most distal portion of the colon.
**TNM staging** International classification analyzing the extent of cancer spread; assessment of tumor, nodal, and metastatic status.

**The rectum is the distal-most aspect of the large intestine, located distal to the sigmoid colon and proximal to the anal canal. The wall of the rectum has four layers: mucosa, submucosa, muscularis propria, and an adventitia or subserosa and visceral peritoneum (present anteriorly along the proximal portion of the rectum at the peritoneal reflection). The rectum is entirely lined by glandular mucosa that is identical to that of the colon. Although these basic characteristics are universally accepted, more precise definitions of the location, extent, and boundaries of the human rectum are surprisingly controversial. Recently, increased interest in rectal anatomy has provoked a great deal of debate; consensus has been sought for standardization of surgical techniques for rectal resection and for data comparisons among clinical studies of rectal disease.**

## CLINICAL IMPORTANCE OF RECTAL ANATOMY

A precise anatomic definition of the rectum is clinically important for at least three reasons. A precise anatomic definition (1) identifies the boundary between the rectum and the anal canal, which determines the appropriate staging system (i.e., colorectal vs. anal canal) for cancers of this region; (2) delineates the lymph nodes that are included in the regional lymphatic drainage and are assigned to the N category, versus those that are nonregional and assigned to the M category in the TNM staging system of the American Joint Committee on Cancer (AJCC) and the Union Internationale Contre le Cancer (UICC); and (3) describes the histologic layers of the viscus, which are directly relevant to the pathologic evaluation of surgical resection specimens and to analysis of circumferential (nonperitonealized, radial) margins.

## PRACTICAL ASPECTS OF RECTAL ANATOMY

The origin of the rectum is marked by several distinctive structural features. At the point of transition from sigmoid colon to rectum, the tenia coli of the sigmoid fuse to form the continuous circumferential layer of the rectal muscularis propria, and the epiploic appendages disappear. It also is at the point of origin of the rectum that the free peritoneal mesentery of the sigmoid colon terminates and the mesorectum begins. The mesorectum, a subperitoneal layer of fibroadipose tissue containing all of the nerves, blood vessels, and regional lymph nodes, is enveloped by a fascia propria. The mesorectum surrounds the rectum for most of its length, ending at the level of the pelvic floor a few centimeters proximal to the termination of the rectum and the beginning of the anal canal. The mesorectal collar is asymmetric, with the bulk of the mesorectal soft tissue lying posterior to the rectum. Anteriorly, the areolar plane that lies external to the mesorectum condenses and the fascia propria of the mesorectum merges with the retrovesical fascia (in the male) or the retrovaginal septum (in the female). Laterally, the merged fascias appear as discrete ligaments, often called the lateral ligaments of the rectum.

The point of termination of the rectum, widely recognized by surgeons as a palpable landmark, is called the anorectal ring. This represents the site of merger of the muscles that form the levator ani (pubococcygeus, ileococcygeus, and puborectalis) with the muscle of the superior aspect of the anal sphincter. Despite these generally accepted anatomic definitions of the origin and termination of the rectum, the boundaries of the rectum are more commonly defined by the more clinically convenient measurements from the anal verge. Given the wide anatomic variation among individual patients of different sexes and body habitus, it is not surprising that definitions based on measurements have not concurred.

## CONTROVERSIES IN DEFINING RECTAL ANATOMY

In *Guidelines for Colon and Rectal Cancer Surgery*, a surgical consensus statement published in 2001, the

 

rectum was defined as being 12 cm or less from the anal verge by rigid proctoscopy, but the distal rectal margin (at the point of transition to the anal canal) was not defined. This definition of the proximal rectal border was considered justifiable on a biologic rather than anatomic basis, because clinical observations indicate that the patterns of recurrence of tumors above 12 cm are more consistent with colonic cancers than rectal cancers. The multidisciplinary Colorectal Common Data Elements Task Force sponsored by the National Institutes of Health and the National Cancer Institute defined the rectum as beginning 12 cm above the perianal skin as measured endoscopically, but the distal boundary was defined as 2 cm above the distal-most aspect of the dentate line. Both of these definitions emphasized measurement from the anal verge, the point of transition from the hair-bearing perianal epidermis to the squamous mucosa of the anal canal, to identify the origin of the rectum. Measurement from the anal verge is itself inherently imprecise due to the considerable anatomic variation of this landmark.

Clinically, a precise definition of the border between the distal rectum and the proximal anal canal is essential because adenocarcinomas of these adjacent regions are staged differently. Specifically, in the TNM staging system for colorectal cancer of the AJCC and UICC, the T category of colorectal cancer is defined by the degree of extension through the wall, and the N category of colorectal cancers is defined by the number of involved nodes. In contrast, the T category (i.e., T1 and T2) of anal canal cancer is defined by tumor size, and the N category is defined by the location of involved nodes. Despite the importance of defining anatomic location for proper staging of distal rectal versus anal canal cancers, the staging literature has been rife with confusing statements. The fifth edition of the AJCC staging manual, on which TNM staging was based from 1998 until January 2003, offered two contradictory descriptions of the rectum. On the one hand, it defined the rectum as the distal 10 cm of large intestine as measured from the anal verge with a sigmoidoscope, but it also stated that the rectum is approximately 12 cm in length, making no allowance for the anal canal.

The revised definition of the rectum offered in the sixth edition of the AJCC staging manual allows for more anatomic variation but is still in conflict with other currently published definitions. In the sixth edition of the manual, the origin of the rectum is described as being variably located from 12 to 15 cm from the dentate line. The definition contrasts with that from the *Guidelines for Colon and Rectal Cancer Surgery* and the *Colorectal Common Data Elements*, in which the origin of the rectum is defined as 12 cm or less from the anal verge or the perianal skin, respectively. Thus, consensus is still lacking, and for the purposes of data comparison, these conflicting definitions are problematic.

By any of these definitions, the border between the rectum and anal canal is not a clear-cut anatomic landmark on visual inspection. In practice, however, physicians may ignore this controversial issue altogether and tend to regard the readily identifiable dentate line as the anorectal border. If it is accepted that the border between the anal canal and rectum is ledge of the anorectal ring, the most proximal aspect of the anal canal is lined by rectal-type glandular mucosa. At the dentate line, a narrow zone of transitional mucosa similar to urothelium also may be present. This proximal zone of the anal canal (i.e., from the top of the panaorectal ring to the dentate line, including the transitional zone) measures approximately 1–2 cm. Thus, the termination of the rectum is actually located 1–2 cm above the dentate line, and tumors with an epicenter located up to 2 cm above the dentate line are staged as anal canal cancers, not rectal cancers.

## CONCLUSION

The rectum begins at the point of fusion of the tenia coli and the termination of the mesosigmoid at the termination of the sigmoid colon. It ends where the anal canal begins, about 1–2 cm above the dentate line. The length of the rectum, measured between these two landmarks, varies among individuals of different sex and body habitus.

### See Also the Following Articles

**Anal Canal • Anal Cancer • Colon, Anatomy • Colorectal Adenocarcinoma • Colorectal Adenomas • Gastrointestinal Tract Anatomy, Overview**

### Further Reading

Fleming, I. D., Cooper, J. S., Henson, D. E., *et al.* (eds.) (1997). Digestive system. *In* "AJCC Manual for Staging of Cancer," 5th Ed., pp. 57–109. Lippincott Raven, Philadelphia.

Greene, F. L., Balch, C. M., Fleming, I. D., *et al.* (eds.) (2002). Digestive system. *In* "AJCC Manual for Staging of Cancer," 6th Ed., pp. 89–164. Springer Verlag, New York.

Nelson, H., Petrelli, N., Carlin, A., *et al.* (2001). Guidelines for colon and rectal cancer surgery. *J. Natl. Cancer Inst.* 93, 583–596.

Stocchi, L., Nyam, D. C. N. K., and Pemberton, J. H. (2002). The anatomy and physiology of the rectum and anus including applied anatomy. *In* "Surgery of the Alimentary Tract" (G. D. Zuidema and C. J. Yeo, eds.), 5th Ed., Vol. IV, pp. 332–356. W. B. Saunders, Philadelphia.

# Recurrent Abdominal Pain (RAP)

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**cognitive behavioral therapy** Therapeutic approach of adding to behavioral interventions (e.g., relaxation and behavior management techniques) strategies such as cognitive restructuring; for example, a therapist may evaluate a patient's cognitive interpretation of bodily sensations and teach how cognition impacts affective experience and behavior.

**functional abdominal pain** Most common cause of recurrent abdominal pain in children (unknown etiology); no specific structural, infectious, inflammatory, or biochemical cause for the abdominal pain can be determined.

**recurrent abdominal pain** Common term in the pediatric literature; refers to paroxysmal abdominal pain that persists for greater than 3 months' duration and affects normal activity.

**visceral hypersensitivity** Increased visceral perception; perceived as pain.

**Recurrent abdominal pain (RAP), a common term in the pediatric literature, refers to paroxysmal abdominal pain in children that persists for longer than 3 months and affects normal activity. RAP has been reported to occur in 10–15% of children between the ages of 4 and 16 years. At least as many children experience chronic pain, but maintain normal activity and rarely come to the attention of the physician. Recurrent abdominal pain is not a singular diagnosis. The differential diagnosis of RAP includes organic pain (anatomical, infectious, inflammatory, and biochemical causes), psychogenic pain, and functional abdominal pain. Although no incidence data are available, clinical experience suggests that by far, the most common cause of RAP is functional abdominal pain. The modifier "functional" is used in gastroenterology if no specific structural, infectious, inflammatory, or biochemical cause for the abdominal pain can be determined. Yet, in clinical practice, functional abdominal pain should not be a diagnosis of exclusion. Primary-care physicians should be able to make a primary diagnosis of functional abdominal pain without resorting to a large battery of biochemical or X-ray tests. Management of functional pain is facilitated by early diagnosis, parental education and reassurance, and clear delineation of goals of therapy. The major outcome variable in management of functional abdominal pain in children is lifestyle, not cure of the pain.**

## DIAGNOSIS OF FUNCTIONAL ABDOMINAL PAIN

One reason why primary-care physicians have difficulty making a positive diagnosis of a functional abdominal pain is that there is rarely a clear distinction between acute and chronic abdominal pain. Primary caregivers must often deal with the evolution of pain from the initial acute presentation to a chronic or recurring problem. A stepwise series of diagnostic studies is often initiated during early stages of the pain when an organic etiology is considered to be more likely. Empiric therapy with nonopioid analgesic medications, antispasmotic/anticholinergic agents, and gastric acid-reducing agents may be tried before time criteria for RAP are met. Parents tend to become more frustrated and anxious, particularly if they perceive a serious disorder is being missed, or if the physician implies that the primary factors that influence the perception of pain are cognitive and emotional. Parental uncertainty only increases the stressful environment, which provokes or reinforces the pain behavior. Thus, the concept of functional abdominal pain must be introduced into the differential diagnosis of abdominal pain in children before the 3-month time criteria for duration of pain are met.

The key variables that point toward a functional diagnosis are a normal physical exam, other than abdominal pressure tenderness, and absence of signs and symptoms that, despite evidence-based verification, are generally accepted to be alarm signals for an organic disorder. None of the following criteria has been shown to discriminate between organic, functional, or psychosomatic disorders: frequency of pain, character of pain, location of pain, pain awakening patient at night, associated gastrointestinal (GI) symptoms (including anorexia, nausea, episodic vomiting, increased gas, or altered bowel pattern), or associated extraintestinal symptoms (including fatigue, headache, and arthralgia). Even with a normal physical exam, further diagnostic testing is definitely indicated in the presence of the following alarm signals: involuntary weight loss, growth retardation, significant vomiting, significant diarrhea, GI blood loss, associated fever, arthritis, rash, symptoms of a psychiatric disorder, or family history of inflammatory

 

bowel disease. Alarm signals in the physical examination include evidence of linear growth deceleration, localized tenderness in the right upper or lower quadrants, localized fullness or mass effect, hepatomegaly, splenomegaly, back or costo-vertebral angle (CVA) tenderness, perianal fissure, fistula, soiling, and guaiac-positive stools.

Diagnostic testing is indicated when alarm signals or abnormal physical findings suggest a high possibility of organic disorder. Diagnostic testing may be considered to reassure the parent, patient, or physician when the most likely diagnosis is functional pain. The physician may also need to do testing to rule out organic disease in the patient when pain continues to severely affect lifestyle despite a functional diagnosis. Establishing a working diagnosis of functional pain and initiating conservative therapy before time criteria are achieved do not preclude an ongoing focused diagnostic workup. Although there are no evidence-based data, clinical experience suggests that subclassifying pain presentations may facilitate choice of testing by narrowing zdifferential diagnosis. Children with abdominal pain may be subclassified by one of three clinical presentations: (1) abdominal pain associated with symptoms of upper abdominal distress, (2) abdominal pain associated with altered bowel pattern, and (3) isolated paroxysmal abdominal pain. The frequent occurrence of upper and lower bowel symptoms in the same patient is not uncommon. Functional abdominal pain should be presented as the most common cause of all three clinical presentations. Synonyms of functional pain that may be useful for individualizing diagnosis in a given patient are functional dyspepsia for pain with upper abdominal symptoms, and irritable bowel syndrome for pain associated with altered bowel pattern. Abdominal migraine is a variant of isolated functional abdominal pain. Diagnostic criteria include three or more episodes of intense, acute midline pain during a 3-month period lasting several hours to days with intervening symptom-free intervals lasting weeks to months. Two of the following features are required for diagnosis: (a) headache during episodes, (b) photophobia during episodes, (c) associated classical unilateral migraine headaches, which may or may not be associated with abdominal pain, (d) family history of migraine, and (e) visual, sensory, or motor aura antedating acute pain.

## DIFFERENTIAL DIAGNOSIS OF SUBCATEGORIES OF ABDOMINAL PAIN

### Abdominal Pain Associated with Symptoms of Upper Abdominal Distress

Symptoms of upper abdominal distress include pain or discomfort localized in the upper abdomen, and pain related to eating, nausea, episodic vomiting, bloating, early satiety, and occasional heartburn and oral regurgitation. Table I lists the differential diagnosis of abdominal pain associated with symptoms of upper abdominal distress. Alarm signals such as anorexia, vomiting, weight loss, and evidence of GI bleeding (hematemesis, melena, occult bleeding) suggest an upper GI inflammatory, infectious, structural, or biochemical disorder. Focused laboratory evaluation should be performed in any patient with historical or physical alarm signals, including complete blood count with differential, erythrocyte sedimentation rate (ESR), *Helicobacter pylori* serology and/or stool antigen, hepatic panel, and pancreatic enzyme measurement. In cases in which recurrent vomiting is a significant part of the history, an upper GI series with small bowel follow-through and abdominal ultrasound should be considered to rule out gastric outlet disorder, malrotation, partial small bowel obstruction, small bowel Crohn's disease, gallstones, pseudocyst, hydronephrosis secondary to ureteropelvic junction (UPJ) obstruction, and retroperitoneal mass. Gastroesophageal reflux disease should be suspected when heartburn or oral regurgitation of sour or bitter gastric contents is prominent parts of the history. Biliary pain is typically episodic, severe, constant pain in the right upper quadrant or epigastrium that persists for 20 minutes to 2 hours, usually triggered by eating. In relapsing pancreatitis, recurrent severe epigastric pain persistent for days and may radiate to the back. Recurrent epigastric or right upper quadrant pain associated with tender hepatomegaly suggests chronic hepatitis. Continuous pain, especially in the context of

**TABLE I Major Differential Diagnosis of Recurrent Abdominal Pain Associated with Symptoms of Upper Abdominal Distress**

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| Functional dyspepsia |
| Gastroesophageal reflux disease |
| Drug-associated GI disorder (NSAID, iron, antibiotic) |
| *Helicobacter pylori* gastritis |
| Peptic ulcer |
| Gastroparesis |
| Eosinophilic gastroenteritis |
| Crohn's disease |
| Obstructive disorders (e.g., malrotation, partial small bowel obstruction) |
| Biliary tract disease (choledocholithiasis, chronic cholecystitis, biliary dyskinesia) |
| Hydronephrosis |
| Chronic hepatitis, sclerosing cholangitis |
| Relapsing pancreatitis/pancreatic pseudocyst |
| Parasitic infection |
| Celiac disease |

multisystem complaints, is an alarm signal for possible psychiatric disease. Eating disorder should also be considered in any young patient with significant weight loss.

In the absence of peptic ulcer disease, the relationship between *H. pylori* infection and abdominal pain remains unclear. Although there are no evidence-based data to establish a clear link *H. pylori* gastritis alone, and abdominal pain associated with symptoms of upper abdominal distress, most gastroenterologists will treat a symptomatic child who has been identified as *H. pylori* positive. The rationale is that *H. pylori* may act as a physical trigger of functional dyspepsia in selected patients. Some clinicians have concluded that the most cost-effective approach is to test serologically for *H. pylori* and to treat all infected cases. However, many investigators have pointed out that commercially available serological assays do not appear to have the necessary sensitivity or specificity to screen pediatric patient populations. Empirical treatment of *H. pylori* should only be considered in patients with elevated immunoglobulin G (IgG) antibody, and is not recommended for patients with positive IgM or IgA antibody. It is not unreasonable to avoid antibody testing completely, and consider treatment only in patients with endoscopically proved infection.

Upper endoscopy should be considered in untreated patients with alarm signals, in patients who fail to respond to time-limited antisecretory therapy, and in patients in whom symptoms recur after the end of treatment. Upper endoscopy is the gold standard to rule out inflammatory disorders in the upper GI tract and to establish a firm diagnosis of functional dyspepsia. Recognizable objective findings by gross endoscopic examination include superficial erosions, ulcer, stricture, antral nodularity associated with *H. pylori* gastritis, gastric rugal hypertrophy associated with Menetrier's and cytomegalovirus (CMV) gastritis, and the small heaped-up, volcanic-like mounds, pocked with a central crater, associated with chronic varioliform gastritis. Objective histologic findings may help to diagnose reflux esophagitis, eosinophilic gastroenteritis, CMV gastritis, *H. pylori* gastritis, Crohn's disease, and celiac disease. In the absence of gross ulcer or histologic evidence of *H. pylori*, superficial antral gastritis or duodenitis are of questionable clinical significance, and should not dissuade a diagnosis of functional abdominal pain. There is no evidence in children that nonspecific superficial antral gastritis or duodenitis progresses to peptic ulcer. Evaluation of gastric emptying by scintigraphy to rule out gastroparesis, and gallbladder function assessment by hepatobiliary scan with ejection fraction, to rule out chronic cholecystitis and biliary dyskinesia, should be considered only after upper endoscopy and consultation by a pediatric gastroenterologist. Endoscopic retrograde cholangiopancreatography is indicated only if there is biochemical or radiological evidence of recurrent pancreatitis, or biliary-type abdominal pain following cholecystectomy.

## Abdominal Pain Associated with Symptoms of Altered Bowel Pattern

Altered bowel pattern may include change in frequency and/or consistency of stools (diarrhea or constipation), pain relief with defecation, straining or urgency, feeling of incomplete evacuation, passage of mucus, or a feeling of bloating or abdominal distension. Table II lists the differential diagnosis of abdominal pain associated with symptoms of altered bowel pattern. In patients with diarrhea, focused laboratory evaluation should include complete blood count with differential, erythrocyte sedimentation rate, stool for ovum parasites, and stool for *Clostridium difficile* toxin. Lactose intolerance should be considered as a potential primary etiology of chronic abdominal pain in the presence of diarrhea. A trial of a lactose-free diet or performance of a lactose breath hydrogen test is prudent in children with pain associated with loose bowels, bloating, and increased flatulence. Alarm signals including evidence of GI bleeding, tenesmus, pain or diarrhea repeatedly wakening the patient from a sound sleep, involuntary weight loss, linear growth deceleration, extraintestinal symptoms (fever, rash, joint pain, recurrent aphthous ulcers), positive family history of inflammatory bowel disease, iron deficiency anemia, and elevated ESR are indications to pursue a diagnosis of inflammatory bowel disease by colonoscopy and upper gastrointestinal (UGI) study with small bowel follow-through. Diarrhea associated with encopresis suggests chronic fecal retention and megacolon. At present, although there are no evidence-based data, serological testing for celiac disease should be considered in patients with pain and altered bowel pattern. Serological testing should

**TABLE II Major Differential Diagnosis of Recurrent Abdominal Pain Associated with Altered Bowel Pattern**

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| Irritable bowel syndrome |
| Chronic infection (parasitic, *Clostridium difficile*) |
| Inflammatory bowel disease (Crohn's disease, ulcerative colitis, microscopic colitis, e.g., lymphocytic colitis, eosinophilic colitis, collagenous colitis) |
| Lactose intolerance |
| Fecal retention/megacolon |
| Drug-associated GI disorder |

definitely be performed in all patients with iron deficiency anemia or secondary amenorrhea. Chronic watery diarrhea is also an indication to pursue colonoscopy to rule out microscopic inflammation, which may alter colonic motility and absorptive function. The large volume of diarrhea (400–1200 g/day) distinguishes patients with microscopic lymphocytic, collagenous, or eosinophilic colitis from those with irritable bowel, for whom stool weight in excess of 300 g/day is rare.

The accuracy of colonoscopy in diagnosing inflammatory conditions of the colon is superior to barium enema because of the direct visualization of the mucosal surface and the ability to obtain biopsy and culture specimens. Intubation of the terminal ileum can also aid in the diagnosis of Crohn's disease. Recognizable objective findings by gross examination with a flexible endoscope include edema, erosions, ulceration, pseudomembranes (discrete yellow plaques on the colonic mucosa), and polyps. Subjective gross endoscopic findings, including erythema, increased vascularity, and spontaneous friability, become meaningful only in the context of histology, because they are subject to more interobserver variation in interpretation. Objective histologic findings include (1) cryptitis, crypt abscesses, and crypt distortion with branching and drop out, suggesting ulcerative colitis or Crohn's disease, (2) noncaseating granuloma specific for Crohn's disease, (3) fibrosis and histiocyte proliferation in the submucosa, suggesting Crohn's disease, and (4) epithelial and intraepithelial lymphocytes or eosinophils, with or without subepithelial collagen thickening in lymphocytic colitis, eosinophilic colitis, and collagenous colitis, respectively. The latter should be considered specific findings only in patients with profuse diarrhea. Mild superficial increases in interstitial lymphocytes or eosinophils in the absence of crypt distortion or significant diarrhea are nonspecific, and should not dissuade the physician from making a positive diagnosis of irritable bowel syndrome.

## Isolated Paroxysmal Recurrent Abdominal Pain

Table III lists the major differential of recurrent paroxysmal periumbilical abdominal pain in children. It is important to try to see the patient during an attack, because it is frequently the only opportunity to assess alarm signals. The Carnett test may help to determine whether pain is arising from the abdominal wall or has an intraabdominal origin. The site of maximum tenderness is found through palpation. The patient is then asked to cross arms and assume a partial sitting position (crunch), which results in tension of the abdominal wall. If there is greater tenderness on repeat palpation in this position, abdominal wall disorders (such as cutaneous nerve entrapment syndromes, abdominal wall hernia, myofascial pain syndromes, rectus sheath hematoma, or costochondritis) should be suspected. Discitis, which is really an osteomyelitis of the vertebral end plate, may present as a combination of back and abdominal pain. The condition is usually associated with intermittent fever, elevated peripheral white blood cell count, and elevated erythrocyte sedimentation rate. Unrecognized constipation should be suspected if a left lower quadrant or suprapubic fullness or mass effect is appreciated on abdominal exam, and rectal exam reveals evidence of firm stool in the rectal vault, or soft stool in a dilated rectal vault with evidence of perianal soiling. Often, a history of constipation or encopresis is unknown to the parent. Parasitic infections, particularly *Giardia lamblia*, *Blastocystis hominis*, and *Dientamoeba fragilis*, may present with chronic pain in children in the absence of altered bowel pattern. Alarm signals, including pain repeatedly awakening the patient from a sound sleep, anorexia, involuntary weight loss, linear growth deceleration, evidence of GI bleeding, and extraintestinal symptoms (fever, rash, joint pain), are also indications to evaluate for Crohn's disease, or rare disorders such as polyarteritis nodosa, intestinal ischemia, eosinophilic gastroenteritis, and angioneurotic edema, which can be indistinguishable from Crohn's disease on clinical grounds. Suspicion of polyarteritis nodosa rests on evidence of extraintestinal disease, particularly renal involvement. Mesenteric vein obstruction should be considered in adolescents using oral contraceptives. Clinically, it can present gradually with progressive abdominal pain over a period of weeks. Pneumatosis is usually a late finding. The clinical presentation of eosinophilic gastroenteritis depends on the depth of the infiltration by the eosinophilic process. Submucosal disease can become manifest with abdominal pain and signs of obstruction.

TABLE III Major Differential Diagnosis of Isolated Recurrent Abdominal Pain

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| Functional abdominal pain |
| Abdominal migraine |
| Intermittent intestinal obstruction (Crohn's disease, malrotation w/wo volvulus, intussusception with lead point, postsurgical adhesions, small bowel lymphoma, eosinophilic gastroenteritis, angioedema) |
| Unrecognized constipation |
| Appendiceal colic |
| Dysmenorrhea (endometriosis, ectopic pregnancy, adhesions from pelvic inflammatory disease) |
| Cystic teratoma of ovary |
| Musculoskeletal disorders (muscle pain, linea alba hernia, discitis) |
| Vascular disorders (mesenteric thrombosis, polyarteritis nodosa) |
| Acute intermittent porphyria |

Any region of the GI tract can be involved. Angioneurotic edema can be heralded by recurrent episodes of pain in the absence of cutaneous or oropharyngeal edema. Family history is usually positive for allergy. Recurrent fever associated with generalized abdominal pain and peritoneal signs suggests the possibility of familial Mediterranean fever. Appendiceal colic is a controversial cause of chronic abdominal pain. Appendiceal spasm has been postulated to be caused by inspissated casts of fecal material within the appendix. A number of anecdotal surgical reports have described complete resolution of pain symptoms following elective appendectomy. Appendiceal colic should be suspected in patients with recurrent acute episodes of well-localized abdominal pain and tenderness, most commonly in the right lower quadrant, demonstrated on several examinations. Dull, midline, or generalized lower abdominal pain at the onset of a menstrual period suggests dysmenorrhea. The pain may coincide with the start of bleeding or may precede the bleeding by several hours. Gynecological disorders associated with secondary dysmenorrhea include endometriosis, partially obstructed genital duplications, ectopic pregnancy, and adhesions following pelvic inflammatory disease. Cystic teratoma has been described in prepubertal patients presenting with right or left lower quadrant pain. The vast majority of such patients have a palpable abdominal mass. Benign ovarian cysts in adolescent females do not cause recurrent abdominal pain. Acute intermittent porphyria (AIP) is a rare disorder characterized by the temporal association of paroxysmal abdominal pain and a wide variety of central nervous system symptoms, including headache, dizziness, weakness, syncope, confusion, memory loss, hallucinations, seizures, and transient blindness. AIP is often precipitated by low intake of carbohydrate or by specific drugs such as barbiturates or sulfonamides.

Laboratory evaluation might include complete blood count (CBC) with differential and ESR to screen for occult systemic inflammatory condition. The decision to do stool ova and parasite exams is dependent on the incidence of *G. lamblia*, *B. hominis*, and *Dientamoeba fragilis* within the community. The most valuable diagnostic test in a patient with symptoms suggesting obstruction is an upper GI series and small bowel follow-through (SBFT). Rare conditions such as lymphoma, angioneurotic edema, mesenteric vein thrombosis with ischemia, eosinophilic gastroenteritis, and pseudo-obstruction will also be suggested by the UGI series. Abdominal ultrasound and abdominal computed tomography (CT) scans have low diagnostic yield for picking up appendiceal abnormalities with recurrent right lower abdominal pain. Colonoscopy and ileoscopy should be performed to rule out Crohn's disease in such patients if blood work or UGI–SBFT suggest the possibility of inflammatory disease. Elective laparoscopy with planned appendectomy should be considered in patients with chronic right lower quadrant pain and negative infectious, inflammatory, and anatomical evaluation. Head CT scan to rule out intracranial space-occupying lesions should be considered in patients with recurrent abdominal pain and headache.

In the absence of historical or physical alarm signals, the diagnosis of functional abdominal pain should be introduced into the differential diagnosis of abdominal pain persisting a month beyond the usual course of an acute disease (e.g., gastroenteritis, urinary tract infection). Parents should be told that a diagnosis of functional pain can be made if duration of pain goes on to exceed 3 months. It is important to provide a brief explanation of visceral hypersensitivity and altered motility, the concept of stress factors, and natural history. Parents should also be told early on that functional pain is difficult to eradicate, and some continuing pain will often have to be accepted by the patient.

## TREATMENT OF FUNCTIONAL ABDOMINAL PAIN

Management of functional abdominal pain begins with a positive diagnosis and an explanation of suspected pathophysiology, natural history, and goals of therapy. Specific treatments include dietary modification, drug therapy, and psychological support. Hospitalization is rarely indicated for patients with functional abdominal pain.

### Positive Diagnosis

Positive diagnosis is based on normal physical examination and absence of alarm signals in the history, as previously described.

### Explanation of Suspected Pathophysiology and Natural History

The exact etiology and pathogenesis of functional abdominal pain in children are unknown. There is general agreement that functional pain is genuine. The prevailing viewpoint is that the pathogenesis of the pain involves visceral hypersensitivity and altered conscious awareness of gastrointestinal sensory input, with or without disordered gastrointestinal motility. Painful sensations may be provoked by physiologic phenomena or concurrent physical and psychological stressful life events. Examples of physiologic phenomena that may trigger pain include postprandial gastric or intestinal

distension, gastric emptying, intestinal contractions of the migrating motor complex, intestinal gas, or gastroesophageal reflux. Intraluminal physical stress factors that may trigger pain include aerophagia, simple constipation, lactose intolerance, minor noxious irritants such as spicy foods, *H. pylori* gastritis, celiac disease, or drug therapy. Systemic physical or psychological stress factors may also provoke or reinforce the pain behavior by altering the conscious threshold of GI sensory input in the central nervous system. Acute or chronic physical illness may unmask functional pain. Psychological stress factors may include death or separation of a significant family member, physical illness or chronic handicap in parents or sibling, school problems, altered peer relationships, family financial problems, or recent geographical relocation.

It is not clear whether the different clinical presentations of functional abdominal pain result from a heterogeneous group of disorders, or represent variable expressions of the same disorder. The frequent occurrence of upper and lower bowel symptoms in the same patient suggests that the latter scenario may indeed be the case. There appears to be a genetic vulnerability because of the high frequency of functional disorders in family members. The fact that most children "outgrow" pain symptoms also suggests that variation of neuroendocrine development may also be a factor in the pathophysiology. In some patients, associated symptoms, including headache, dizziness, motion sickness, pallor, temperature intolerance, and nausea, suggest a generalized dysfunction of the autonomic nervous system. Sex, intelligence, and personality traits do not distinguish patients with functional pain from those with organic pain. The majority of patients are of average intelligence. The generalization that patients with functional abdominal pain are superintellects, perfectionists, over-achievers, bad social mixers, or constant worriers is without foundation. However, there are some data suggesting that the incidence of functional gastrointestinal disorders may be higher in patients with mental diagnoses, such as attention-deficit disorder/hyperactivity, anxiety, depression, school phobia, posttraumatic stress, bipolar disorder, autism, and eating disorders.

The morbidity associated with functional abdominal pain is rarely physical, but results from interference in normal school attendance and performance, peer relationships, participation in organizations and sports, and personal and family activities. Only 1 in 10 children with functional abdominal pain attend school regularly, and absenteeism is greater than 1 day in 10–28% of patients. A common misconception is that pain is the direct cause of the morbidity. In fact, focus on symptom relief by parents, school, and physicians reinforces the pain behavior with attention at the time of pain, rest periods during pain, tactile stimulation and medication to alleviate pain symptoms, and absence from school on days of pain. This approach fails to reinforce nonpain responses, such as normal activity. Although pain does not originate from its consequences, ongoing pain behavior is often accounted for and modified by its consequences.

## Goals of Therapy

The focus of treatment is not "cure" of pain, but rather management of symptoms and adaptation to illness. Goals of treatment include regular school attendance, school performance to the child's ability, participation in desired extracurricular activities, normal weight gain and growth, and normal sleep pattern.

## Dietary Modification

The role of dietary modifications in the management of functional pain disorders is not established. Postprandial symptoms in functional dyspepsia may be improved by eating low-fat meals or by ingesting more frequent but smaller meals throughout the day. High-fiber diet is recommended for both diarrhea-predominant and constipation-predominant irritable bowel and isolated functional pain. The goal for fiber intake in grams is calculated by adding the patient's age +5. Excessive fiber in the diet may result in increased gas and distension, actually provoking pain. Malabsorption of dietary carbohydrates may act as provocative stimuli in functional abdominal pain. Most often, the patient does not perceive a temporal association between ingestion of a particular sugar and the abdominal pain. Avoidance of excessive intake of milk products (lactose), carbonated beverages (fructose), dietary starches (corn, potatoes, wheat, oats), or sorbitol-containing products (vehicle for oral medication, sugar substitute in gum and candy, ingredient in toothpaste, and a plasticizer in gelatin capsules) is not unreasonable. Conformation of lactose intolerance by a lactose breath hydrogen test should be considered before recommending prolonged lactase enzyme replacement therapy or commercial milk products that have been pretreated with lactase enzyme. Excessive gas in patients with irritable bowel syndrome (IBS) can be managed by advising the patient to eat slowly, to avoid chewing gum, and to avoid excessive intake of

carbonated beverages, legumes, foods of the cabbage family, and foods or beverages sweetened with aspartame.

## Drug Therapy

There are no evidence-based data on the effects of pharmacological therapy in pediatric patients with functional abdominal pain. Antispasmodic agents, including hyoscyamine, dicyclomine, glycopyrrolate, peppermint oil, and calcium-channel blockers, are commonly used in clinical practice to treat visceral abdominal pain, although efficacy is unproved. Time-limited (8 weeks) empirical medical therapy with a histamine-2 (H2) blocker or proton pump inhibitor (PPI) is an acceptable diagnostic test of self-limiting upper GI inflammation in patients with abdominal pain and symptoms of dyspepsia. If possible, it is prudent to stop nonsteroidal antiinflammatory drugs (NSAIDs), iron preparations, and antibiotics such as erythromycin or tetracyclines in a patient complaining of upper abdominal discomfort. After a firm diagnosis of functional dyspepsia is established by upper endoscopy, it is not unreasonable to continue acid inhibition therapy in patients who initially responded to shot-term empiric treatment, but had recurrence of pain symptoms with attempts at step-down therapy. Short-term step-up to a PPI may be tried in patients who previously did not respond to an H2 blocker. In adults, sucralfate, a drug that stimulates mucosal prostaglandin synthesis and release of cytokines and has cytoprotective properties, has been reported to be superior to placebo and H2 blocker in alleviating symptoms of dyspepsia. Prokinetic therapy has also been reported in adults to provide superior symptom improvement compared to placebo, especially in patients with dysmotility-like dyspepsia in which the predominant complaint is an unpleasant discomfort in the upper abdomen characterized by upper abdominal fullness, nausea, early satiety, or bloating. At present, metoclopramide is the only option for treating pediatric patients. Metoclopramide has a significant side-effect profile, including drowsiness, dystonic reactions, and increased prolactin levels. As stated previously, although *H. pylori* eradication therapy is not established to be effective in adults with functional dyspepsia, the available data clearly do not rule out the possibility. Thus, most pediatric gastroenterologists still recommend treating documented *H. pylori* in conjunction with endoscopic-established functional dyspepsia.

There are also no evidence-based data on the effects of pharmacological therapy in pediatric patients with irritable bowel syndrome. Synthetic opioids such as loperamide and diphenoxylate are effective in treating IBS-associated diarrhea. Loperamide is preferred over diphenoxylate because it does not traverse the blood–brain barrier. Nonstimulating laxatives such as polyethylene glycol solution, mineral oil, milk of magnesia, and lactulose are effective adjuncts in treating constipation-predominant IBS.

Although formal randomized placebo-controlled trials are lacking, there has been a recent surge in using antidepressant and psychotropic agents to treat both diarrhea-predominant IBS and functional dyspepsia in adults. Anecdotally, this class of drugs appears to be effective in adults with or without psychiatric abnormalities, especially low-dose tricyclic antidepressants. These drugs may act as "central analgesics" to raise perception threshold for abdominal pain to or down-regulate pain receptors in the intestine. There are as yet no data on treatment of pediatric patients. For adults, there has been a recent surge in the development of novel drugs for IBS, including 5-hydroxytryptamine isotype 3 (5-HT3) receptor antagonists, 5-hydroxytryptamine isotype 4 (5-HT4) receptor agonists, and κ-opioid agonists, aimed at restoring normal visceral sensation. Significant beneficial effect of the 5-HT3 antagonist alosetron has been reported in diarrhea-predominant adult women with IBS. Significant beneficial effect of the 5-HT4 agonist tegaserod has been reported in constipation-predominant adult women with IBS. None of these drugs has been studied in children.

## Psychological Support

The first goal is to identify, clarify, and possibly reverse psychological stress factors that may have an important role in onset, severity, exacerbations, or maintenance of pain. Equally important is to reverse environmental reinforcement of the pain behavior. Parents and school must be engaged to support the child rather than the pain. Regular school attendance is essential regardless of the continued presence of pain. In many cases, it is helpful for the physician to communicate directly to school officials to explain the nature of the problem. School officials must be encouraged to be responsive to the pain behavior but not to let it disrupt attendance, class activity, or performance expectations. Within the family, less social attention should be directed toward the symptoms. Consultation with a child psychiatrist or psychologist may be indicated when there is concern about maladaptive family coping mechanisms, or if attempts at environmental modification do not result in return to a normalized lifestyle.

Many patients and parents are unable or unwilling to report emotional states or acknowledge a relationship between psychogenic stresses and pain symptoms. It is best to limit discussion of psychological issues to what the patient and family can accept and let the physician/patient/family relationship evolve by continuing to listen actively, provide empathy, and educate about potential benefit of relaxation techniques and coping strategies. Referral for psychological treatment can be proposed as part of a multispecialty treatment package to help the patient manage the pain symptoms better. It is critical that the psychologist or psychiatrist initially focus on illness behavior and expand psychotherapeutic treatments as indicated only as the patient or parents begin to see the benefits of referral.

Cognitive behavioral therapies add strategies such as cognitive restructuring to behavioral interventions such as teaching relaxation and behavior management techniques. For example, a therapist would evaluate a patient's cognitive interpretation of bodily sensations and teach how cognition impacts affective experience and behavior. The perception that abdominal pain is a sign of impending physical disease must be countered, both to address functional disability and to reassure the family that a functional diagnosis is credible. Attribution styles can also be examined for distortions. Patients are taught to treat their beliefs as hypotheses to be tested, rather than accept their beliefs as inherently valid. Cognitive behavioral interventions targeting children's competence in social roles may be a useful adjunct to other medical treatment in reducing illness behavior. In addition, parents are trained to behaviorally reinforce appropriate coping behavior. Evidence-based data show that cognitive behavioral treatment helps to reduce pain and improve functioning. Cognitive behavioral treatment has been compared to standard pediatric care, and both groups demonstrate reductions in pain at 3 months; however, those receiving cognitive behavioral treatment are more likely to be pain free at 6-month (55.6 vs. 23.8%) and 12-month followup (58.8 vs. 36.8%) evaluations. These findings are very encouraging, although replication by different investigators is still needed.

### Hospitalization

During hospitalization, 50% of patients experience relief of symptoms. However, no data have been presented that the natural history of the pain is affected. Hospitalization does not enhance the fundamental goals of environmental modification. More commonly, it will reinforce pain behavior.

## PROGNOSIS OF RECURRENT FUNCTIONAL ABDOMINAL PAIN IN CHILDREN

There are no prospective studies of the outcome of any of the various presentations of functional abdominal pain. Once functional abdominal pain is diagnosed, subsequent followup rarely identifies an occult organic disorder. Interestingly, pain resolves completely in 30–50% of patients by 2–6 weeks after diagnosis. This high incidence of early resolution suggests that child and parent accept reassurance that the pain is not organic and that environmental modification is effective treatment. Nevertheless, more long-term studies suggest that 30–50% of children with functional abdominal pain in childhood experience pain as adults, although in 70% of such individuals, the pain does not limit normal activity. Of patients with functional abdominal pain, 30% develop other chronic complaints as adults, including headaches, backaches, and menstrual irregularities. Based on a small number of patients, Apley and Hale have described several factors that adversely influence prognosis for a lasting resolution of pain symptoms during childhood, including male sex, age of onset less than 6 years, strong history of a "painful family," and greater than 6 months elapsed time from onset of pain symptoms to established functional diagnosis.

### See Also the Following Articles

**Carbohydrate and Lactose Malabsorption • Celiac Disease, Pediatric • Colitis, Ulcerative (Pediatric) • Cow Milk Protein Allergy • Crohn's Disease, Pediatric • Gastritis and *Helicobacter pylori*, Pediatric • Gastroesophageal Reflux Disease (GERD) and Congenital Esophageal Obstructive Lesions, Pediatric • Intussusception • Irritable Bowel Syndrome • Malrotation • Parasitic Diseases, Overview • Volvulus**

### Further Reading

Apley, J. (1975). The child with abdominal pains. Blackwell Scientific Publ., London.

Boyle, J. T. (1997). Recurrent abdominal pain: An update. *Pediatr. Rev.* **18**, 310–321.

Rasquin-Weber, A., Hyman, P. E., Cucchiara, S., Fleisher, D. R., Hyams, J. S., Milla, P. J., and Staiano, A. (1999). Childhood functional gastrointestinal disorders. *Gut* **45**(Suppl. II), II60–II68.

Walker, L. S., Guite, J. W., Duke, M., Barnard, J. A., and Greene, J. W. (1998). Recurrent abdominal pain: A potential precursor of irritable bowel syndrome in adolescents and young adults. *J. Pediatr.* **132**, 1010–1015.

Sanders, M. R., Shepard, R. W., Cleghorn, G., and Woolford, H. (1994). The treatment of recurrent abdominal pain in children: A controlled comparison of cognitive behavioral family intervention and standard pediatric care. *J. Consult. Clin. Psychol.* **62**, 306–314.

# Rotavirus

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**hemagglutinin** The viral protein that binds to erythrocytes.
**Jennerian** Regarding vaccines, the use of naturally attenuated but antigenically similar animal strains as human vaccines, as Jenner used cowpox virus to protect against smallpox.
**positive and negative strands** The coding sequence and the complementary antisense sequence, respectively.
**RNA polymerase** The viral enzyme needed to replicate the double-stranded RNA viral genome in the mammalian host.

**In 1972, a virus was first implicated as a cause of human gastroenteritis. Rotaviruses are now identified as the leading cause of severe dehydrating gastroenteritis in infants and children.**

## CLASSIFICATION

The rotavirus genus is contained within the family *Reoviridae*. Viral particles are 1020 Å in diameter and consist of two protein capsids surrounding a central protein core that contains the genome. Ten monocistronic segments and one bicistronic genomic segment form the double-stranded RNA genome. Rotavirus appears in electron microscopy as a sharply defined rim to which spokes radiate from a large central hub, thus suggesting the name from the Latin *rota*, meaning wheel.

## HOST RANGE AND VIRUS PROPAGATION

Animal strains rarely infect humans, although human isolates that probably are derived from feline, canine, bovine, or porcine rotaviruses have been described. The potential of animal reservoirs as a source of genetic diversity for the evolution of new human strains is unknown.

## GENETICS

The double-stranded RNA genes distribute by size into four classes that produce a characteristic pattern when separated by polyacrylamide gel electrophoresis. The RNA itself is not infectious; rotaviruses contain an endogenous RNA-dependent RNA polymerase that transcribes the gene segments into mRNA. Transcripts are full-length positive strands from which negative-strand synthesis occurs following the formation of replicase particles in the cytoplasm.

Genes 5, 7, 8, 10, and 11 code for nonstructural proteins known as NSP1–5, but functional roles are incompletely understood. Genes 1–4, 6, and 9 code for structural proteins VP1–4, 6, and 7, respectively. VP4 and VP7 are the two surface proteins of the virion and VP6 is the major constituent of the second protein layer.

## SEROLOGIC RELATIONSHIPS

VP6 bears most of the common group antigens. Group A rotaviruses cause most human disease. The glycoprotein VP7 is the viral tinin, an important determinant of virulence, and VP4 is the cell attachment protein. VP7 and VP4 are used in the serologic classification of rotaviruses. The VP7 serotype is classified as a G (glycoprotein) type and the VP4 type as a P (protease) type. Fourteen G types and 20 P types have been distinguished, many in humans. However, the relationship of serotype to protective immunity is not entirely clear. For instance, immunoglobulin A (IgA) anti-VP6 may mediate intracellular viral neutralization and particles containing only VP2 and VP6 have induced protective immunity in animals.

## EPIDEMIOLOGY

Group A rotaviruses are the principal cause of severe gastroenteritis in infants and young children, accounting for one-third of all diarrheal episodes requiring hospitalization in children under the age of 2 years. In developing countries, the annual toll includes roughly 18 million cases of severe diarrhea and nearly a million deaths. Infants in the first 2 to 3 months of life are relatively protected from severe disease, probably because of residual maternal transplacental antibodies. Rotavirus infections occur beyond 3 years of age and

 

into adult life but are typically mild or asymptomatic. Human illness occurs in the cooler months in developed countries, peaking in January and February. This seasonality does not occur in tropical climates where rotavirus infections occur throughout the year.

Rotaviruses are transmitted by the fecal–oral route. Rapid appearance of antibodies to rotaviruses is noted by 3 years of age in all areas of the world regardless of hygiene. Asymptomatic infection occurs frequently in newborn nurseries and day-care centers. The virus is quite stable on environmental surfaces for prolonged periods. These factors complicate the control of hospital outbreaks.

## CLINICAL FEATURES OF INFECTION

The incubation period is 24–72 h. Malnutrition may increase the severity of the symptoms. Diarrhea, vomiting, and fever are usually noted. Symptoms related to severe volume depletion such as lethargy, irritability, confusion, and eventually vascular collapse and death can be seen.

## PATHOLOGY AND HISTOPATHOLOGY

Villus blunting and vacuolation of columnar intestinal epithelial cells occur within hours after infection. Distended endoplasmic reticulum, mitochondrial swelling, and denuded microvilli are also seen together with mononuclear cell infiltration of the lamina propria. Viral particles may be seen within columnar epithelial cells, goblet cells, phagocytic cells, and M cells. Intestinal morphology returns to normal in approximately 7 days.

Diarrhea is not clearly related to histologic damage. NSP4 may have toxin-like effects that induced diarrhea in mice by stimulation of chloride secretion. Water absorption is impaired, but is ameliorated by glucose–salt solutions. Abnormal motility may contribute to vomiting and diarrhea. Carbohydrate malabsorption and secondary osmotic diarrhea may occur. An integrated view of pathogenesis of diarrhea has not yet been achieved.

## IMMUNE RESPONSE

The immune response to infection includes serum and mucosal antibodies that are thought to be important in the prevention of subsequent infections. Cytotoxic T cells have been identified in the intestinal mucosa. The rapid resolution of acute infection occurs before the immune response is fully developed, so some of the factors responsible for resolution of the illness appear to be unrelated to acquired T- and B-cell immunity.

## TREATMENT AND PREVENTION

Effective treatment of rotavirus diarrhea is accomplished with oral rehydration with glucose and electrolyte solutions. Logistical and educational difficulties limit this treatment in underdeveloped areas. Vaccination strategies have utilized the host range restrictions of animal rotaviruses in a "Jennerian" approach to disease prevention. Unfortunately, increased rates of intussusception immediately after vaccination caused withdrawal of the only commercially marketed attenuated rotavirus vaccine.

### See Also the Following Articles

**Diarrhea, Infectious • Gastroenteritis • Nosocomial Infections**

### Further Reading

Desselberger, U., Iturriza-Gomara, M., *et al.* (2001). Rotavirus epidemiology and surveillance. *Novartis Found. Symp.* 238, 125–147, discussion 147–152.

Lundgren, O., and Svensson, L. (2001). Pathogenesis of rotavirus diarrhea. *Microbes Infect.* 3, 1145–1156.

Offit, P. A. (2002). The future of rotavirus vaccines. *Semin. Pediatr. Infect. Dis.* 13, 190–195.

Patton, J. T. (2001). Rotavirus RNA replication and gene expression. *Novartis Found. Symp.* 238, 64–77, discussion 77–81.

# Roux Stasis Syndrome

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**denervation** Cutting of a nerve.
**vagotomy** Division of the vagus nerve.

**The Roux stasis syndrome is a motility disorder of the residual stomach and proximal jejunum following partial gastric resection and Roux-en-Y gastrojejunostomy. Characterized by abdominal pain, epigastric fullness, nausea, and vomiting of food (rather than bile), the syndrome develops in up to 30% of patients with Roux-en-Y gastrojejunostomy. Careful history and diagnostic imaging distinguish these postgastrectomy complaints from those of efferent loop obstruction, bile reflux gastritis, or mechanical obstruction.**

## ALTERATIONS IN ANATOMY AND PHYSIOLOGY

The Roux-en-Y reconstruction following partial gastric resection is named for the Finnish surgeon Cesar Roux. Duodenal and proximal jejunal secretions join the fecal stream through a jejunojejunostomy made at least 40 cm distal to the gastrojejunostomy. The iatrogenic denervation abnormalities of both the stomach and Roux limb may contribute to development of the syndrome.

Vagotomy is often done with gastric resection to avoid complications of ulceration at the anastomosis, but may impair gastric compliance, gastric emptying, and jejunal contractions. Duodenal pacing of proximal jejunal contractions is interrupted by the creation of the Roux limb, resulting in fewer depolarizations in the limb, with resultant stasis. Ectopic pacemakers in the limb propagate in both directions, compounding the motility disorder. Phase III contractions, which normally are intense motor impulses thought to be helpful in clearing indigestible material from the lumen of the jejunum, are not as effective or as regular in the Roux limb as in the nonoperated jejunum.

## TREATMENT OF THE ROUX STASIS SYNDROME

Endoscopy, barium studies, and scintigraphic measute of gastric emptying are used to exclude mechanical obstruction. The treatment of choice is resection of all but a small portion of the gastric cardia and creation of a new gastrojejunostomy. At the time of revision, the Roux limb is measured and shortened if longer than 40 cm (Fig. 1). To make the Roux limb shorter than this predisposes to reflux of bile and pancreatic secretions.

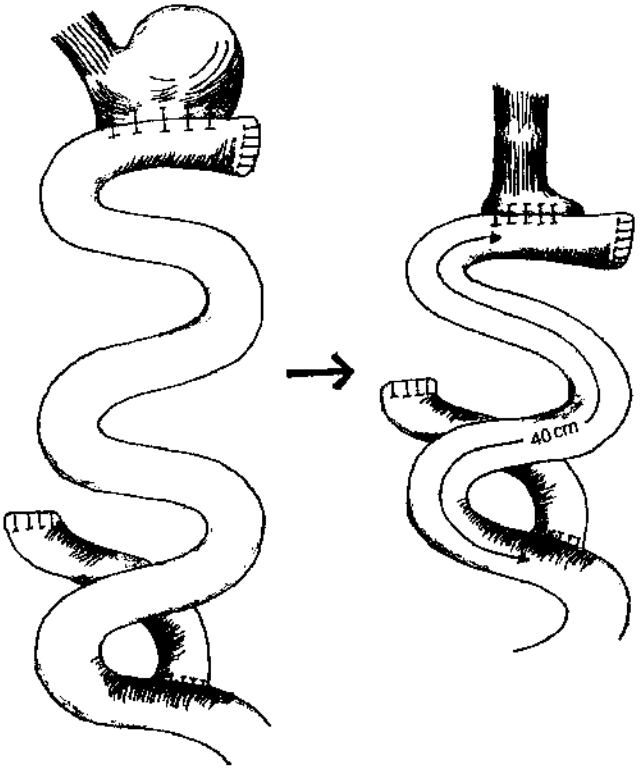


**FIGURE 1** Roux-en-Y reconstruction after resection of a portion of the stomach is revised such that only a small portion of proximal stomach remains. The jejunal Roux limb between the two anastomoses is shortened such that it is less than 40 cm long.

More than 80% of patients gain weight after the revisional procedure; failures are likely due to sustained and irreversible abnormalities of the Roux limb pacing and mechanical clearing mechanisms.

### See Also the Following Articles

Gastric Emptying • Gastroenterostomy

 

## Further Reading

Eagon, J., Miedama, B., and Kelly, K. (1992). Post-gastrectomy syndromes. *Surg. Clin. North Am.* 72(2).

Gustavsson, S., Ilstrup, D. M., Morrison, P., and Kelly, K. A. (1988). Roux-Y stasis syndrome after surgery. *Am. J. Surg.* 155, 490–494.

Miedema, B. (1992). The Roux stasis syndrome: Treatment by pacing and prevention by use of an "uncut Roux limb." *Arch. Surg.* 127, 295–300.

Sawyers, J. (1990). Management of post-gastrectomy syndromes. *Am. J. Surg.* 159, 8–14.


# Rumination Syndrome


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**pathognomonic** Characteristic or indicative of a disease; denoting especially one or more typical symptoms, findings, or pattern of abnormalities specific for a given disease and not found in any other condition.

**Rumination syndrome is characterized by the regurgitation of undigested food and liquids, usually within 15 minutes after eating. Once the regurgitant reaches the mouth, the person can consciously choose to reswallow or expel it. Rumination syndrome is believed to be psychological in origin, which is supported by the absence of organic disease and the link seen between a traumatic or stressful "triggering event" and the onset of symptoms.**

## INTRODUCTION

Historically, rumination syndrome, the spontaneous regurgitation of undigested food and liquids shortly after ingestion, has not been associated with nausea, abdominal pain, heartburn, or nocturnal symptoms; however, more recent studies have found that these symptoms may be present to varying degrees in this syndrome. Due to lack of familiarity with the disease, physicians often confuse rumination syndrome with gastroparesis, gastroesophageal reflux disease, functional esophageal motility disturbances, and eating disorders. Rumination syndrome can be diagnosed solely by taking a careful clinical history, though performing a 4-hour gastric emptying test to rule out gastroparesis is appropriate. Although rumination syndrome has no cure, relaxation therapy is thought to be the most effective form of treatment at this time.

## EPIDEMIOLOGY

Rumination syndrome can affect both sexes at any age. Researchers disagree about whether it is more prevalent in men or women or if it is seen equally in both. Though rumination syndrome occurs in children and adults of normal intelligence, it has been widely studied among infants and people with mental retardation. In fact, it has been estimated that 6–10% of mentally challenged persons in institutions ruminate. The prevalence of the syndrome among people of normal intelligence is difficult to estimate because these patients often do not seek medical attention or are misdiagnosed due to physician unawareness of the disorder.

## DIAGNOSIS

The diagnostic criteria for rumination syndrome are based on evaluation of the patient for the following symptoms, which occurred for at least 12 weeks, not necessarily consecutive, in the preceding 12 months:

1. Persistent or recurrent regurgitation of recently ingested food into the mouth with subsequent remastication and reswallowing or expulsion.
2. Absence of nausea and vomiting.
3. Cessation of the process when the regurgitated material becomes acidic.
4. Absence of pathologic gastroesophageal reflux, achalasia, or other motility disorder with a recognized pathologic basis as the primary disorder.

The key to diagnosing rumination syndrome is to look for the characteristic regurgitation of food and liquids within 15 minutes of eating and the absence of any organic disease. The ability to regurgitate water within minutes of drinking is almost pathognomonic. Though the above criteria state otherwise, nausea can be an associated symptom. However, this feeling is usually brief or comes as a "wave" before the regurgitation. Patients do not awake with nausea or remain chronically nauseated between regurgitation events. Additional symptoms may include abdominal pain (typically in the epigastrium), bloating, fatigue, dehydration, heartburn, belching, and weight gain or loss (though many ruminators maintain a stable weight). The abdominal pain may actually represent the effects of retching or vomiting on the rectus abdominus muscle. Rumination syndrome is distinguished from gastroparesis by the fact that patients with gastroparesis bring up food that is hours or days old, whereas rumination syndrome patients bring up completely undigested food within minutes. In addition, patients with gastroparesis should have a delayed gastric emptying test (GET), whereas rumination syndrome patients should have a normal GET. A full 4-hour GET must be employed to obtain a reliable reading. Rumination syndrome is differentiated from gastroesophageal reflux disease (GERD) by the absence of nocturnal symptoms frequently seen in GERD. Furthermore, patients with rumination syndrome may discontinue ruminating once the stomach contents become acidic, whereas GERD patients may experience acidic reflux for hours. In addition, during the actual postprandial events, rumination patients do not experience heartburn because the acidic contents of the stomach are well buffered by accompanying foods and liquids.

## PATHOPHYSIOLOGY

The physiological mechanism underlying rumination in animals is centered on reverse peristalsis of the esophagus. Because humans are incapable of this activity, three theories have been proposed to explain the rumination phenomena in humans. The first theory states that rumination is due to the simultaneous increase in abdominal pressure and relaxation of the lower esophageal sphincter. This theory has been supported by upper gastrointestinal manometry studies that show a characteristic manometry pattern linking rumination events with simultaneous pressure waves caused by an increase in intraabdominal pressure. The second theory similarly describes a relaxation of the lower esophageal sphincter, but states that it is a voluntary action. The third theory attributes the mechanism of ruminating as an adaptation of the belch reflex.

## TREATMENT

Though rumination syndrome has no cure, various treatment therapies exist that may provide substantial relief. The most commonly recommended treatment is relaxation therapy. Patients should attend several sessions with a clinical psychologist to learn effective relaxation techniques. This involves thinking about a relaxing topic or image, diaphragmatic breathing and meditation, or maintaining a "pseudohypnotic" concentration state for the minutes immediately following eating or drinking. Once the patient learns these techniques, he or she must practice them independently, oftentimes after every meal to control consciously the urge to regurgitate. Other therapies include psychological therapy, behavioral therapy, biofeedback therapy, and a change of diet. These treatments, especially when combined with relaxation therapy, may provide significant relief. Although the rumination events may not be completely eradicated, they may be reduced to occurring only occasionally, or only during certain stressful situations. Finally, education of the patient, family, friends, and school or work personnel is key. Associates should be informed that rumination is a "reflex" or habit that is being addressed. They can be reassured that the patient is not pregnant, does not have a malignancy, or an undiagnosed disease.

### See Also the Following Articles

**Achalasia • Anorexia Nervosa • Belching • Bulimia Nervosa • Emesis • Gastric Emptying • Gastroesophageal Reflux Disease (GERD) • Nausea**

### Further Reading

Clouse, R., and Richter, J. (2000). "Rumination Syndrome. Rome II: The Functional Gastrointestinal Disorders" (D. Drossman, E. Corazziari, N. Talley, W. Thompson, and W. Whitehead, eds.), 2nd Ed., pp. 258–263. Degnon Associates, McLean, Virginia.

Malcolm, A., Thumshirn, M., Camilleri, M., and Williams, D. (1997). Rumination syndrome. *Mayo Clin. Proc.* 72, 646–652.

O'Brien, M., Bruce, B., and Camilleri, M. (1995). The rumination syndrome: Clinical features rather than manometric diagnosis. *Gastroenterology* 108, 1024–1029.

Soykan, I., Chen, J., Kendall, B., and McCallum, R. (1997). The Rumination syndrome: Clinical and manometric profile, therapy, and long-term outcome. *Dig. Dis. Sci.* 42(9), 1866–1872.

Tougas, G., Eaker, E., McCallum, R., *et al.* (2000). Assessment of gastric emptying using a low fat meal: Establishment of international control values. *Am. J. Gastroenterol.* 95(6), 1456–1462.

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# Salivary Glands, Anatomy and Histology

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**acini** Secretory end-pieces that have an approximately spherical shape.
**demilunes** Crescent-shaped groups of serous secretory cells at the ends of mucous end-pieces.
**excretory ducts** Largest ducts in salivary glands running in the interlobular connective tissue and conveying saliva to the mouth.
**intercalated ducts** Small ducts in salivary glands connecting the secretory cells to larger striated ducts.
**intercellular canaliculi** Finger-like projections of the end-piece lumen extending between adjacent secretory cells.
**lumen** Central space of an end-piece into which saliva is secreted; continuous with the lumina of the duct system.
**mucous cells** Salivary gland secretory cells that produce a viscous saliva containing highly glycosylated mucins.
**myoepithelial cells** Contractile cells with branching processes surrounding end-pieces; their contractions force saliva from the end-pieces into the ducts.
**serous cells** Salivary gland secretory cells that produce a watery saliva rich in proteins with enzymatic or antimicrobial functions.
**striated ducts** Intralobular salivary ducts with a striated appearance due to membrane infoldings and aligned mitochondria; active in electrolyte secretion and absorption.

The salivary glands are a collection of three paired major and many minor glands located in and around the oral cavity. Together they produce saliva, a watery fluid that lubricates and protects the oral hard and soft tissues and facilitates taste reception, mastication, swallowing, and speech. The initial, or primary, saliva, including most of the organic components and essentially all of the fluid, is formed by secretory cells organized into secretory end-pieces. The primary saliva is modified by duct cells constituting a series of convergent tubes that eventually form a single large excretory duct that empties into the oral cavity. Secretory end-pieces may be composed solely of serous cells that produce watery saliva rich in proteins and glycoproteins, many of which have enzymatic, antimicrobial, or protective functions, or mucous cells that produce a viscous saliva containing highly glycosylated mucins. Serous secretory end-pieces, or acini, usually are spherical in shape, whereas mucous secretory end-pieces typically are tubular in shape and usually are larger than serous end-pieces. The blind ends of mucous end-pieces frequently are capped by a crescent of serous cells, termed a demilune. Considerable variability exists in the histology and cellular secretory products among glands and species. This article focuses on human salivary glands and rodent salivary cells as the latter are used most often in studies of salivary function.

## HUMAN SALIVARY GLANDS

In humans, there are three paired major salivary glands, located extraorally, and several hundred smaller minor salivary glands, located in the lips, cheeks, tongue, palate, fauces, and retromolar areas. The parotid gland is located subcutaneously, lying over the masseter muscle, just in front of the ear, with a deeper portion extending behind the ramus of the mandible. Its duct, Stensen's duct, runs anteriorly, crossing the masseter muscle and entering the oral cavity at the parotid papilla on the buccal mucosa, opposite the maxillary second molar. The blood supply of the parotid comes from branches of the external carotid artery and the parasympathetic nerve supply is mainly from the glossopharyngeal nerve (cranial nerve IX) via the otic ganglion and the auriculotemporal nerve. The sympathetic innervation of all of the salivary glands is provided by postganglionic fibers from the superior cervical ganglion, traveling with the blood supply.

The submandibular gland is located in the submandibular triangle, below the mylohyoid muscle, with its posterior portion wrapped around the posterior border of the mylohyoid and extending anteriorly for a short distance. Its duct, Wharton's duct, travels anteriorly below the mucosa of the floor of the mouth, opening at the sublingual caruncle. The blood supply of the submandibular gland comes from the facial and lingual arteries and the parasympathetic nerve supply is mainly from the facial nerve (cranial nerve VII), through the lingual nerve and submandibular ganglion.

The sublingual gland, the smallest of the major glands, is located in the floor of the mouth, medial to the mandible and just above the mylohyoid muscle. Its

 

main duct, Bartholin's duct, opens with the duct of the submandibular gland at the sublingual caruncle. Several smaller ducts of the sublingual gland, the ducts of Rivinus, open separately along the sublingual fold in the floor of the mouth. The blood supply of the sublingual gland comes from the sublingual and submental arteries and the parasympathetic innervation is derived from the facial nerve (cranial nerve VII), via the lingual nerve and submandibular ganglion.

The parotid gland contains only serous secretory end-pieces. The intercalated ducts typically are long and the striated ducts are prominent. The submandibular gland (Fig. 1A) is a mixed gland, with both serous and mucous secretory end-pieces; however, the serous end-pieces predominate. The mucous end-pieces are capped by serous demilune cells. The intercalated ducts also are relatively long and the striated ducts are prominent. The sublingual gland (Fig. 1B) also is a mixed gland, consisting predominantly of mucous end-pieces and serous demilunes; few, if any, serous end-pieces are present. The intercalated ducts are short and relatively few striated ducts are present.

The minor salivary glands consist of small aggregates of secretory end-pieces and ducts, located in the submucosal layer of the oral mucosa or between muscle fibers of the tongue. The ducts typically open directly onto the oral mucosal surface. Most of the minor glands are mucous and some include a serous cell component arranged as occasional demilunes. The one exception is the lingual serous (von Ebner's) gland, located in the posterior part of the tongue. Von Ebner's gland is a pure serous gland and its ducts open into the troughs surrounding the circumvallate papillae and at the rudimentary foliate papillae on the sides of the tongue.

## SALIVARY GLAND HISTOLOGY

### Serous Cells

Serous cells (Figs. 1A and 2A) are pyramidal in shape, with the basal surface forming an interface with the extracellular matrix and the apical surface forming a portion of a small lumen that is continuous with the first part of the duct system. Intercellular canaliculi, small finger-like projections of the lumen that increase the lumenal surface area, extend along the lateral cell surfaces toward the bases of the cells. Adjacent cells are held together at their apical ends and along the intercellular canaliculi by junctional complexes consisting of a tight junction, an adhering junction, and one or more desmosomes. Occasional gap junctions also are present on the lateral cell surfaces. The nucleus usually is spherical and is located in the basal half of the cell.

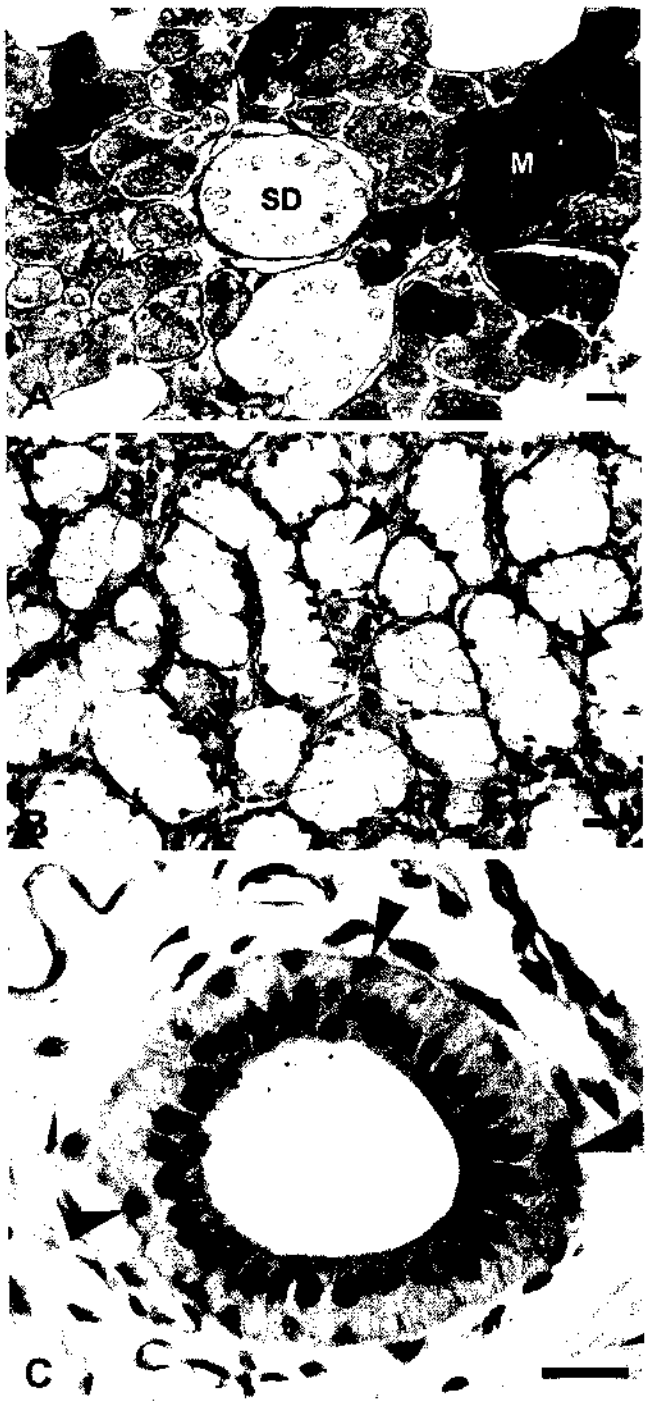


FIGURE 1 Light micrographs of human salivary glands. Scale bars, 20 μm. (A) Submandibular gland, stained with periodic acid-Schiff (PAS)/Alcian blue/hematoxylin. Serous cells, with spherical basal nuclei, contain magenta-staining secretory granules. Mucous cells (M), arranged in tubular secretory end-pieces, are filled with dark red- to purple-staining mucin. Two intercalated ducts (arrowheads), with small cuboidal cells at their junction with the secretory end-pieces, and two striated ducts (SD), with pale-staining columnar cells, are present. Basement membranes around the end-pieces and ducts are stained with PAS. Fat cell

The basal cytoplasm is filled with rough endoplasmic reticulum (RER), a well-developed Golgi complex lies apical or lateral to the nucleus, and the apical cytoplasm is filled with membrane-bound secretory granules, approximately 1 μm in diameter. The granules of human serous cells typically exhibit a bi- or tripartite structure, with an electron-dense core that may be eccentrically located in the granule and one or more regions of lower electron density constituting the remainder of the content. Immunolabeling studies have demonstrated that at least some secretory proteins are differentially distributed in the granule content. Mitochondria, lysosomes, and peroxisomes also are found scattered throughout the cell. Actin filaments usually are associated with the tight and adhering junctions and form a web beneath the apical cell membrane and intermediate filaments are associated with desmosomes as well as with hemidesmosomes that attach the cells to the basal lamina. Microtubules often are present in the Golgi region and the supranuclear cytoplasm. On stimulation, the secretory granules fuse with the lumenal membrane, releasing their contents, which are dissolved in the aqueous fluid transported into the lumen by the cells.

## Mucous Cells

Mucous cells (Figs. 1B and 2B) are large cells shaped like a truncated pyramid. The apex of the cell has a larger lumenal surface than serous cells, but intercellular canaliculi usually are not present between mucous cells. They are joined to their neighbors by junctional complexes and gap junctions. The nucleus is oval in shape, contains denser chromatin than serous cells, and usually is located adjacent to the basal plasma membrane. The RER is present mainly in the basal cytoplasm and a large Golgi complex is located apical or lateral to the nucleus. The apical cytoplasm contains mucous secretory granules that typically are irregular in shape and have a pale content, with some fine granular or filamentous material. The membranes of the granules often are disrupted and/or fused with those

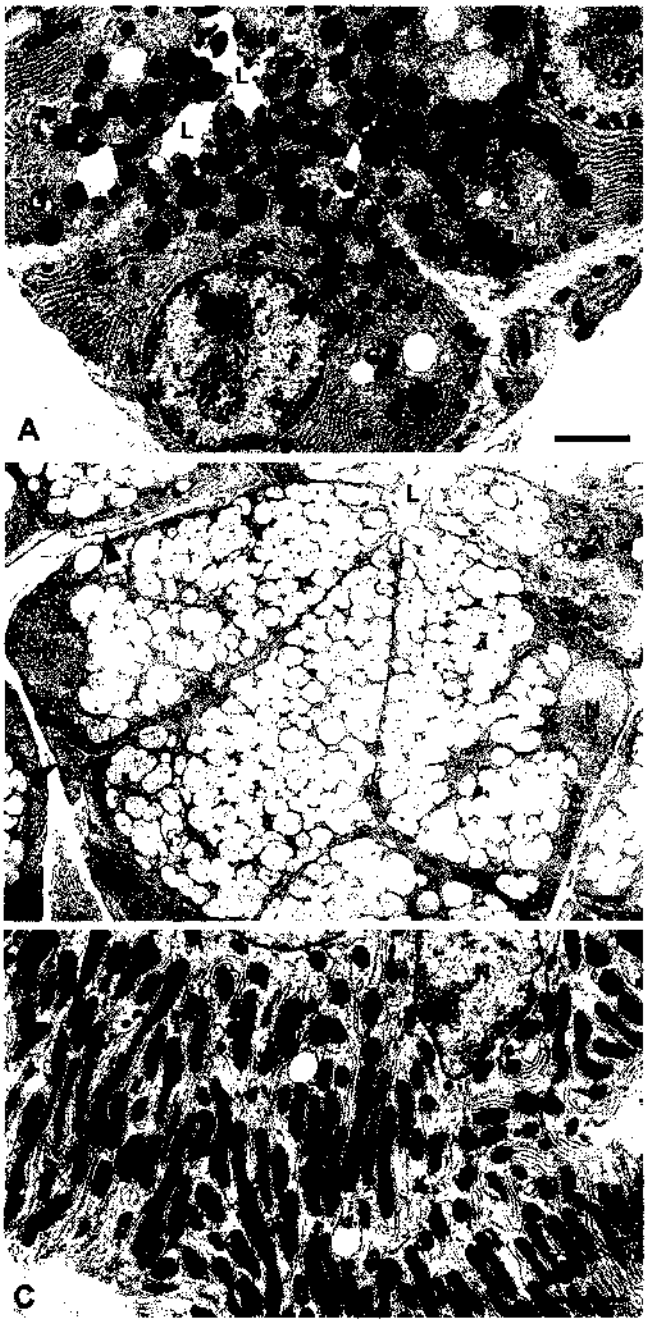


FIGURE 2 Electron micrographs of rodent salivary glands. Scale bars, 2.0 μm. (A) Rat parotid gland end-piece. Serous secretory cells have a basally located spherical nucleus (N), abundant RER, prominent Golgi complexes (G), and electron-dense secretory granules. L, lumen. (B) Mouse sublingual gland end-piece. Several mucous secretory cells are filled with electron-lucent mucous granules, which compress the nuclei (N) against the basal cell membrane. Myoepithelial cell processes (arrowheads) are located along the bases of the secretory cells. L, lumen. (C) Mouse parotid gland striated duct cell. The basal cell membranes of the striated duct cells are extensively folded and numerous elongated mitochondria are present in the cytoplasm between the membranes. Glycogen deposits and a few small dense lysosomes also are present. N, nucleus.

spaces are seen at the edges of the field. From Hand, A. R. (1986). "Oral Histology: Inheritance and Development," (D. V. Provena and W. Seiebel, eds.). 2nd Ed., Lea & Febiger. Copyright Lippincott Williams & Wilkins. (B) Sublingual gland, stained with hematoxylin and eosin (H&E). Mucous cells, with dense basally located nuclei and pale-staining mucin, are arranged in tubular end-pieces with large lumina (arrowheads). Few serous cells are visible. (C) Submandibular gland, stained with H&E. A small excretory duct, with a large lumen, is lined by a pseudostratified epithelium of tall columnar cells and several small basal cells (arrowheads). Numerous small blood vessels are present in the surrounding interlobular connective tissue.

of adjacent granules. This appearance of the mucous granules is believed to be an artifact induced by chemical fixation, which results in a loss of $Ca^{2+}$, disaggregation of the content, an increase in osmotic pressure, and an influx of water that causes granule swelling. Mucins constitute the main product of these cells; few other macromolecules are known to be secreted by mucous cells and the rate of fluid secretion is much lower than for serous cells.

## Myoepithelial Cells

Myoepithelial cells are contractile cells associated with the secretory end-pieces. They are branching or stellate-shaped cells with processes containing actin and myosin that embrace the secretory cells (Fig. 2B). Although their structural and functional characteristics are similar to those of smooth muscle cells, myoepithelial cells are derived from epithelium and reside on the epithelial side of the basal lamina. The myoepithelial cells provide support for the secretory cells and their contraction helps to expel saliva from the end-pieces into the ductal system. Myoepithelial cells also provide signals to the secretory cells that help to maintain cell polarity and the organization of the end-piece and they produce proteins with tumor suppressor activity, such as proteinase inhibitors and anti-angiogenesis factors.

## Ducts

The ductal system consists of three main subdivisions. The first type of duct is the intercalated duct, which connects the secretory end-pieces to the second part of the duct system, the striated duct. Intercalated ducts are the smallest ducts; the cells are low cuboidal (Fig. 1A) and have a relatively simple structure with a few RER cisternae, a small Golgi complex, and, in cells close to the end-pieces, a few secretory granules. The ducts draining several end-pieces typically converge to form a larger intercalated duct that connects to the striated duct. Myoepithelial cells may be located at the basal side of the intercalated ducts; often they have a fusiform shape and are oriented lengthwise along the duct and their processes extend onto the end-piece. Intercalated ducts are thought to participate in the formation of primary saliva, including the fluid component as well as specific organic products such as lysozyme and lactoferrin. In some species, intercalated duct cells have a relatively high mitotic rate and it is thought that they may house a stem cell capable of differentiation into other gland cell types.

Striated ducts (Figs. 1A and 2C) constitute the main intralobular component of the duct system. The duct cells are columnar, with centrally placed nuclei, abundant mitochondria, lysosomes, peroxisomes, and frequently some small apical vesicles and/or secretory granules. They have only small amounts of RER but may have some smooth endoplasmic reticulum in the apical cytoplasm. Their most characteristic feature is the presence of extensive infoldings of the basal and lateral plasma membranes that interdigitate with similar folds of neighboring cells (Fig. 2C). Elongated mitochondria are present in the cytoplasmic partitions between the folds. Striated duct cells function to modify the primary saliva secreted by the end-pieces, principally by reabsorption and secretion of electrolytes. The apical and basolateral membranes contain a number of ion channels and transporters and $Na^+$,$K^+$-ATPase is abundant in the basolateral membrane. The duct cells also secrete kallikrein, which is stored in the apical granules, and the cells are capable of endocytosing foreign proteins introduced into the ductal lumen.

As the ducts leave the gland lobules and enter the interlobular connective tissue, they are called excretory ducts (Fig. 1C). These ducts typically have a pseudostratified epithelium, with columnar cells that resemble the striated duct cells in morphology and function and small basal cells that presumably are undifferentiated cells capable of division and that serve to replace the columnar cells. Tuft cells, or brush cells, which probably have some type of sensory function, and dendritic (antigen-presenting) cells, which function in the immune response, also are found in the excretory ducts. Mucous goblet cells also may be present. As the excretory ducts increase in size, the epithelium may become stratified cuboidal or stratified columnar. Near the oral opening, the main excretory duct frequently is lined by a stratified squamous epithelium.

## Connective Tissue, Vessels, and Nerves

The glands are surrounded by a connective tissue capsule, which extends into the gland as septa, dividing it into lobes and lobules. Finer partitions of connective tissue surround the ducts and end-pieces within the lobule. Collagen and elastic fibers, along with glycoproteins and proteoglycans typical of other connective tissues, constitute the extracellular matrix components, whereas fibroblasts, mast cells, plasma cells, macrophages, and dendritic cells, as well as occasional polymorphonuclear leukocytes and lymphocytes, constitute the cellular components. The blood vessels and nerves that supply the secretory end-pieces and ducts also are present in the connective tissue. The vessels and nerves enter at the hilus of the gland, branching to follow the excretory ducts to the lobules. Within the lobules,

the vessels break up into capillary plexuses around the striated ducts and end-pieces. The nerves, which are unmyelinated postganglionic sympathetic and parasympathetic axons that are enveloped by Schwann cells, exhibit two different types of relationships with the secretory cells. In the most common pattern, termed extraparenchymal, as the nerve bundle approaches a secretory cell, one or more axons exhibit a swelling or varicosity containing a few mitochondria and a cluster of neurotransmitter vesicles. The Schwann cell covering usually is absent at these sites, but the axon remains separated from the secretory cells by approximately 0.1–0.2 μm and by the basal laminae surrounding the nerve bundle and the secretory cell. In the other pattern, termed intraparenchymal, an axon leaves the nerve bundle, penetrates the basal lamina around the secretory cell, and makes close contact (10–20 nm) with the secretory cell. Both types of innervation are effective in stimulating secretion. In most glands, the secretory cells are innervated by both sympathetic and parasympathetic nerves. It is unknown, however, whether every cell is contacted by a nerve. Because the secretory cells are joined by gap junctions, it seems likely that the secretory stimulus spreads from cell to cell and that each secretory end-piece is a functional unit.

## See Also the Following Articles

**Digestion, Overview • Gastrointestinal Tract Anatomy, Overview • Salivary Glands, Physiology**

## Further Reading


Hand, A. R. (1990). The secretory process of salivary glands and pancreas. *In* "Ultrastructure of the Extraparietal Glands of the Digestive Tract" (A. Riva and P. M. Motta, eds.), pp. 1–17. Kluwer Academic, Boston, MA.

Hand, A. R. (2003). Salivary glands. *In* "Ten Cate's Oral Histology" (A. Nanci, ed.), 6th Ed., Mosby, St. Louis, MO, in press.

Hand, A. R., Pathmanathan, D., and Field, R. B. (1999). Morphological features of the minor salivary glands. *Arch. Oral Biol.* 44, S3–S10.

Lantini, M. S., Proto, E., Puxeddu, P., Riva, A., and Testa Riva, F. (1990). Fine structure of excretory ducts of human salivary glands. *J. Submicrosc. Cytol. Pathol.* 22, 465–475.

Pinkstaff, C. A. (1979). The cytology of salivary glands. *Int. Rev. Cytol.* 63, 141–261.

Riva, A., and Riva-Testa, F. (1973). Fine structure of acinar cells of human parotid gland. *Anat. Rec.* 176, 149–165.

Riva, A., Motta, G., and Riva-Testa, F. (1974). Ultrastructural diversity in secretory granules of human major salivary glands. *Am. J. Anat.* 139, 293–298.

Riva, A., Tandler, B., and Testa Riva, F. (1988). Ultrastructural observations on human sublingual gland. *Am. J. Anat.* 181, 385–392.

Riva, A., Testa-Riva, F., Del Fiacco, M., and Lantini, M. S. (1976). Fine structure and cytochemistry of the intralobular ducts of the human parotid gland. *J. Anat.* 122, 627–640.

Riva, A., Valentino, L., Lantini, M. S., Floris, A., and Testa Riva, F. (1993). 3D-structure of cells of human salivary glands as seen by SEM. *Microsc. Res. Tech.* 26, 5–20.

Tandler, B., and Erlandson, R. A. (1972). Ultrastructure of the human submaxillary gland. IV. Serous granules. *Am. J. Anat.* 135, 419–433.

Young, J. A., and van Lennep, E. W. (1978). "The Morphology of Salivary Glands." Academic Press, London.

# Salivary Glands, Physiology

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**acetylcholine** The major neurotransmitter mediating the secretion of saliva, which is initiated by the parasympathetic nervous system.

**acinus** The proximal grape-shaped end-piece in exocrine salivary glands composed of secretory cells that produce essentially all of the fluid and the major portion of the protein content of saliva.

**mucus cells** Salivary gland cells that synthesize, store, and secrete large amounts of mucins.

**muscarinic receptors** Receptors for acetylcholine present in salivary gland cells that act to increase intracellular $Ca^{2+}$.

**myoepithelial cells** Contractile cells that surround acinar structures in salivary glands; their contraction accelerates the expulsion of saliva.

**$Na^+/K^+/2Cl^-$ cotransporter** The major membrane protein mediating uptake of $Cl^-$ across the salivary acinar cell basolateral membrane.

**parotid glands** The major serous salivary glands located bilaterally under the ear.

**serous acinar cells** Salivary acinar cells, which secrete a high volume of water and enzymes.

**xerostomia** The subjective feeling of dryness of the mouth, usually associated with diminished or arrested salivary secretion.

**Normal salivary gland function is essential for providing lubrication during chewing and swallowing of food, for maintaining the hydration of hard and soft oral tissues, and for protecting against mechanical and bacterial insults. Correspondingly, salivary gland dysfunction is associated with an increased incidence of oral disease, which subsequently is often linked to systemic disease. Several million Americans suffer from some form of oral dryness (xerostomia). Most xerostomia is a consequence of head and neck irradiation to treat tumors, Sjögren's syndrome (an autoimmune disease), or drug therapy. Hundreds of prescribed medications interfere with normal salivary gland function, frequently acting at the receptor level. In approximately 10% of dry mouth cases, the underlying etiology is idiopathic. In these cases, xerostomia is likely related to a genetic defect in either water and ion transporter proteins or in a key signaling pathway. An initial step in the development of treatments for xerostomia requires an appreciation of salivary gland physiology.**

## INTRODUCTION

The secretion of saliva involves the coordinated activation of a diverse array of glandular structures, each of which delivers its own exocrine and fluid secretory constituents into the oral cavity. Three "major" pairs of salivary glands (parotid, submandibular, and sublingual) are linked to the oral cavity through relatively long excretory ducts. In addition, localized just under the oral epithelium are numerous smaller "minor" glands, named according to their anatomical locations (i.e., labial, lingual, palatal, buccal, and minor sublingual). This article will focus on highlighting the current understanding of regulatory processes mediating secretion of fluid and exocrine products from these various glands. The focus will mainly be on results from human and rodents, as the latter are the current major animal models in use.

## VARIATIONS AMONG GLANDS IN INNERVATION AND THE RELATIONSHIP TO SECRETION

### General Concepts of Central and Autonomic Control

Salivary glands form a network of secretory units that, depending on the stimulus or insult, react to provide an appropriate combination of secretory products. In general, secretory responses are controlled by complex interactions between the central and autonomic nervous systems. Glands receive postganglionic autonomic fibers to activate specific constituent secretory cells and/or to regulate blood flow. Preganglionic parasympathetic nerve fibers emanate from salivatory centers in the medulla oblongata (i.e., the inferior and superior salivatory nuclei) to synapse in multiple ganglia with postganglionic fibers that innervate the different salivary glands. Postganglionic fibers feeding the submandibular and sublingual glands emanate primarily from the submandibular ganglion. Parotid glands receive postganglionic fibers from the otic ganglion and minor glands are innervated via fibers from the

 

sphenopalatal ganglion or submandibular ganglion. There are no distinct sympathetic salivary centers, although preganglionic fibers emerge from the initial two thoracic segments of the spinal cord and ascend via the sympathetic trunk to synapse in the superior cervical ganglion. Postganglionic fibers follow along with arteries to supply each gland.

Regions within the central nervous system can influence the salivary centers in a positive or a negative manner. For example, the negative influences of central regions on salivary centers are responsible for a dry mouth during periods of emotional stress. Conversely, positive influences on salivary centers are likely responsible for increased salivation in response to appropriate smells or to the anticipation of feeding or vomiting. Reflex secretion in response to gustatory (taste) or mechanical (mastication and touch) stimuli appears to be controlled more by localized neural feedback loops that involve input from lingual taste receptors and periodontal mechanoreceptors, respectively. The broad distribution of diverse glands supplying the oral cavity provides for different reflex stimuli to influence the nature of the final secretion, in both protein and fluid content. Secretion can also be localized more to a general site within the oral cavity, such as in the case of a unilateral chewing stimulus and the resultant dominant parotid secretory response on the same side.

The pattern of autonomic innervation to cellular elements is not necessarily similar between glands or between species for the same gland. In general, postganglionic parasympathetic fibers are abundant in all major and minor salivary glands examined to date. In addition, acetylcholine (ACh) efferent fibers near blood vessels and ducts also contain vasoactive intestinal peptide (VIP), peptide with N-terminal histidine and C-terminal isoleucine (PHI), substance P (SP), and calcitonin gene-related peptide (CGRP). Only VIP and possibly enkephalins are co-localized with Ach in fibers around acini, although SP is also present in the rat. In addition to norepinephrine, sympathetic fibers near blood vessels contain neuropeptide Y. Sympathetic fibers to vascular, ductal, and acinar elements may also contain enkephalins.

## Parotid and Submandibular Glands

In parotid glands, adrenergic and cholinergic postganglionic fibers are associated with serous acinar exocrine cells, intercalated ducts, large vascular structures, myoepithelial cells, and striated ducts. Submandibular glands have a similar pattern of innervation, despite marked species differences in acinar cell types. Human submandibular acini are primarily serous with a small proportion of mucous tubuloacini, whereas in rodents, submandibular acini are uniformly seromucous and secrete a low-molecular-weight mucin. Parasympathetic stimulation to either parotid or submandibular glands results in limited acinar cell degranulation accompanied by profuse fluid secretion. Conversely, sympathetic activation produces little fluid output and extensive acinar cell degranulation.

## Mucous Glands

The major sublingual glands of mice, rats, and humans as well as the minor sublingual, buccal, and labial glands in humans have a rich supply of cholinergic nerves to acinar elements and blood vessels. These glands have a more sporadic cholinergic innervation of ducts. Adrenergic innervation is localized primarily to blood vessels and is absent or barely detectable within acini. Because all these glands contain abundant mucous tubuloacini usually capped by serous (seromucous) demilune cells, other minor mucous glands (palatal and lingual mucous glands) are likely innervated in a similar fashion. Mucous glands also undergo reflex secretion (e.g., gustatory stimulation, chewing, and speaking) as demonstrated in human labial glands. Both fluid secretion and exocrine secretion by mucous acinar cells are controlled primarily by muscarinic cholinergic receptors. Exocrine secretion by mucous cells, *in vitro*, is also responsive to VIP but to a maximal response that is less than half of the muscarinic-induced response. Unlike mucous cells, the exocrine response of demilune cells appears unresponsive to parasympathetic stimulation or muscarinic agonist but is instead stimulated by β-adrenergic agonists. Whether demilune cells contribute a fluid component to assist in the flow of viscous mucins has been speculated upon but has yet to be demonstrated. The serous lingual glands of von Ebner also undergo exocytosis in response to muscarinic agonist or parasympathetic nerve activation. Sympathetic fibers may function in a similar manner, although results are conflicting.

## Myoepithelial Cells

Myoepithelial cells that surround all acinar structures (rat parotid is an exception) as well as intercalated ducts contract on stimulation of parasympathetic fibers (via muscarinic receptors) and, when present, sympathetic fibers (via α-adrenergic receptors). Contraction initially accelerates the expulsion of saliva and is then thought to provide support against increased intralumenal pressures during secretion. Gap junctions between myoepithelial and acinar cells likely function

in intracellular communications and may help to propagate a neurostimulus.

### Innervation of Blood Vessels and Control of Blood Flow

There is a complex integration between signals to activate secretion and blood flow to specific glands. The volume of secretion during parasympathetic salivation is related directly to the glandular venous pressure through the opening of arteriovenous anastomoses. Simultaneous arteriolar dilation further assists to elevate capillary hydrostatic pressure. Both acetylcholine and VIP are vasodilatory and function synergistically, whereas sympathetic vasomotor fibers can counteract these effects through α-adrenergic mechanisms. Moreover, nitric oxide synthase (NOS) is localized to postganglionic parasympathetic nerves feeding vascular elements in submandibular glands and functions to enhance the release of VIP and reduce the degradation of VIP-induced cyclic AMP (cAMP) in vascular smooth muscle. In contrast, NOS is mostly absent in sympathetic postganglionic nerves. Afferent sensory fibers of unknown function are also localized to blood vessels and occasionally to ducts within all three major glands. These fibers originate in the trigeminal ganglion and display immunoreactivity to CGRP, neurokinin A, and SP. Because not all elements within a gland are thought to be activated simultaneously during normal reflex responses, perhaps afferent fibers provide feedback of blood flow and/or pressure to help regulate localized reflex secretory responses.

## G-PROTEIN-COUPLED RECEPTORS AND INTRACELLULAR SIGNALING IN SALIVARY ACINAR CELLS

### General Aspects

Salivary glands possess an abundance of receptor types that, in general, reflect the pattern of autonomic innervation to each gland. Two signaling pathways, calcium and cyclic AMP, and the receptors responsible for their initiation have historically been the primary focus of studies to elucidate secretory responses of salivary cells to various neurotransmitters. However, in the past decade multiple isoforms of receptors, intracellular signaling molecules, and components of fluid/exocrine secretory pathways have been identified. As the annotation of mammalian genomes progresses, many more isoforms and/or splice variants will likely be revealed. As specific isoforms of these molecules are identified in salivary cells, the task of characterizing functional signaling pathways becomes even more complicated, especially when multiple and operationally equivalent isoforms are expressed. Furthermore, it is becoming increasingly apparent that cells utilize macromolecular complexes for the temporal–spatial localization, efficiency, and integration of signaling pathways. Therefore, delineating such complexes and their functions represents a formidable quest in current and future salivary research.

### Calcium Signaling

Acetylcholine from postganglionic parasympathetic nerves stimulates acinar cell muscarinic cholinergic receptors. There are five subtypes of muscarinic receptors (M1–5) and acinar cells of the major glands (probably all minor glands as well) express abundant M3 muscarinic receptors. Additionally, mucous cells of sublingual and possibly minor glands also express significant M1 muscarinic receptors (equivalent to M3 receptor levels) and recent data raise the possibility of the M5 receptor subtype in salivary glands. M1 and M3 receptors couple predominantly to $G_q$ and $G_{11}$ G-proteins to activate (via the $G_\alpha$ subunit) phosphatidylinositol 1,4-bisphosphate (PIP2)-specific phospholipase C (PLC). The $\beta_3$ isoform of PLC is present in rat parotid glands. PLC hydrolyzes plasma membrane PIP2 to release diacylglycerol and inositol 1,4,5-trisphosphate ($IP_3$). In rodent parotid and submandibular acinar cells, $IP_3$ initiates a rapid increase in the intracellular free calcium ($[Ca^{2+}]_i$) by opening $IP_3$-sensitive $Ca^{2+}$ channels (260 kDa $IP_3$ receptor glycoproteins in tetrameric form) within components of the endoplasmic reticulum (ER) localized in the apical cytoplasm. Depletion of internal $Ca^{2+}$ stores activates the influx of extracellular $Ca^{2+}$ through a storage-operated $Ca^{2+}$ entry mechanism in the plasma membrane that has yet to be defined, although evidence suggests a role for *trp* (transient receptor potential) gene products. These $Ca^{2+}$ release and influx mechanisms function in concert with $Ca^{2+}$ pumps to regulate $[Ca^{2+}]_i$ in a temporal–spatial manner to produce either oscillation or waves of increases in $[Ca^{2+}]_i$ in response to muscarinic receptor activation. These $Ca^{2+}$ pumps are localized in the plasma membrane to extrude intracellular $Ca^{2+}$ as well as SERCA (sarco-endoplasmic reticulum $Ca^{2+}$) pumps in the ER to refill $Ca^{2+}$ stores. The pattern of oscillatory or wave-like changes in $[Ca^{2-}]_i$ is the result of multiple factors that are the focus of intense investigation. Such factors likely include (1) the spatial distribution of SERCA pumps (isoforms 3 and 2b); (2) expression levels and distribution of $IP_3$ receptor isoforms that display various sensitivities to $IP_3$ and are also regulated by $Ca^{2+}$ levels in both the ER stores

and cytosol; and (3) contributions from ryanodine receptors that also function as $Ca^{2+}$-release channels within ER membranes and are controlled by multiple mechanisms including $[Ca^{2+}]_i$ and phosphorylation by serine/threonine kinases. All five $IP_3$ receptor isoforms and ryanodine type III receptors are expressed in mouse parotid glands.

Acinar cells of rodent parotid and/or submandibular glands also express $\alpha_1$-adrenergic receptors ($\alpha_{1a} > \alpha_{1b}$ isoforms) and substance P receptors (two isoforms of the tachykinin $NK_1$ receptor) that on receptor activation produce an increase in $[Ca^{2+}]_i$ presumably through coupling to $G_{q/11}$ proteins and to downstream mechanisms similar to M3 receptors. Possible receptor-specific patterns of oscillatory or wave-like changes in $[Ca^{2+}]_i$ have yet to be defined. It must be noted that extrapolating results of rodent tachykinin receptors to human receptors may not be warranted given the low levels of substance P innervation to acinar cells in human major and minor glands. Furthermore, studies of rodent sublingual and human labial glands suggest the absence of $\alpha_1$-adrenergic receptor in mucous cells.

Four different P2 nucleotide receptor subtypes ($P2X_7$, $P2X_4$, $P2Y_1$, and $P2Y_2$) are present in salivary glands. $P2X_7$ and $P2X_4$ receptors are ATP-gated non-selective cation channels that increase $[Ca^{2+}]_i$ when activated. $P2X_7$ receptors can also form pores for molecules up to 900 Da. $P2Y_1$ receptors (ADP-selective) and $P2Y_2$ receptors (UDP-selective) couple to $G_{q/11}$ proteins to increase $[Ca^{2+}]_i$ and are expressed at very low levels in normal glandular tissues. Interestingly, glandular $P2Y_2$ receptors are up-regulated in response to injury, suggesting a role in cell renewal.

### Signaling via Cyclic AMP

Acinar cells of parotid and submandibular glands express β-adrenergic receptors ($\beta_1$ and $\beta_2$ isoforms) coupled via $G_s$-proteins to activate adenylyl cyclase, increasing intracellular cAMP and subsequently stimulating cAMP-dependent protein kinase A (PKA). In contrast, only serous demilune cells, not mucous cells of sublingual glands, express β-adrenergic receptors. Multiple isoforms of adenylyl cyclase (3, 5/6, and 8) and PKA regulatory subunits (isoforms I and II) are present in rodent parotid and submandibular glands. Although PKA type II is predominantly expressed, both isoforms are associated with identical catalytic subunits and are activated on β-adrenergic receptor stimulation. Acinar cells of all three major glands express VIP receptors also linked to $G_s$-proteins to activate adenylyl cyclase. Adrenergic $\alpha_{2A}$ receptors are present both pre- and postsynaptically in rodent major salivary glands. These receptors are coupled to $G_i$ G-proteins and may either inhibit adenylyl cyclase or activate PLC, although their function in salivary glands has not been extensively explored.

## ACINAR CELL FLUID SECRETION

### Fluid and Electrolyte Secretion Mechanisms

Fluid secretion is driven by transepithelial $Cl^-$ movement (Fig. 1). Salivary gland acinar cells secrete an isotonic, plasma-like fluid. This primary fluid is subsequently modified in a gland-specific manner as it passes through the duct system (e.g., NaCl reabsorption, $K^+$ secretion, additional protein secretion). The opening of $K^+$ and $Cl^-$ channels in the basolateral and apical membranes, respectively, of acinar cells initiates the secretion process. Simultaneous activation of these two types of channels permits $Cl^-$ to exit across the lumenal membrane and loss of $K^+$ into the interstitial fluid, creating a lumen negative transepithelial potential difference. This transepithelial electrical potential difference leads to passive $Na^+$ passage across tight junctions. The resulting lumenal NaCl accumulation and transepithelial osmotic gradient drive the movement of water, creating a plasma-like primary secretion. Water channels expressed in acinar cells are important for transcellular water transport and the generation of saliva.

Sustained $Cl^-$-dependent fluid secretion requires a robust $Cl^-$ reuptake mechanism. The primary $Cl^-$ uptake pathway is the $Na^+/K^+/2Cl^-$ cotransporter located in the basolateral membrane. This mechanism concentrates intracellular $Cl^-$ four to five times above its electrochemical gradient and is up-regulated many fold during sustained stimulation. Paired $Cl^-/HCO_3^-$ and $Na^+/H^+$ exchangers are also located in the basolateral membrane of acinar cells and significantly contribute to saliva formation. The energy required for $Cl^-$ uptake via the cotransporter and the paired exchangers is stored in the inward-directed $Na^+$ chemical gradient created by $Na^+$ pumps.

### Muscarinic Cholinergic Stimulation of Fluid Secretion

Parasympathetic stimulation of fluid secretion has been studied mostly in parotid acinar cells. The dominant mechanism producing fluid secretion is the muscarinic-induced increase in acinar $[Ca^{2+}]_i$ with subsequent activation of $Ca^{2+}$-gated $K^+$ and $Cl^-$ channels. The fluid secretion model shown in Fig. 1 places the $Ca^{2+}$-dependent $K^+$ and $Cl^-$ channels in the

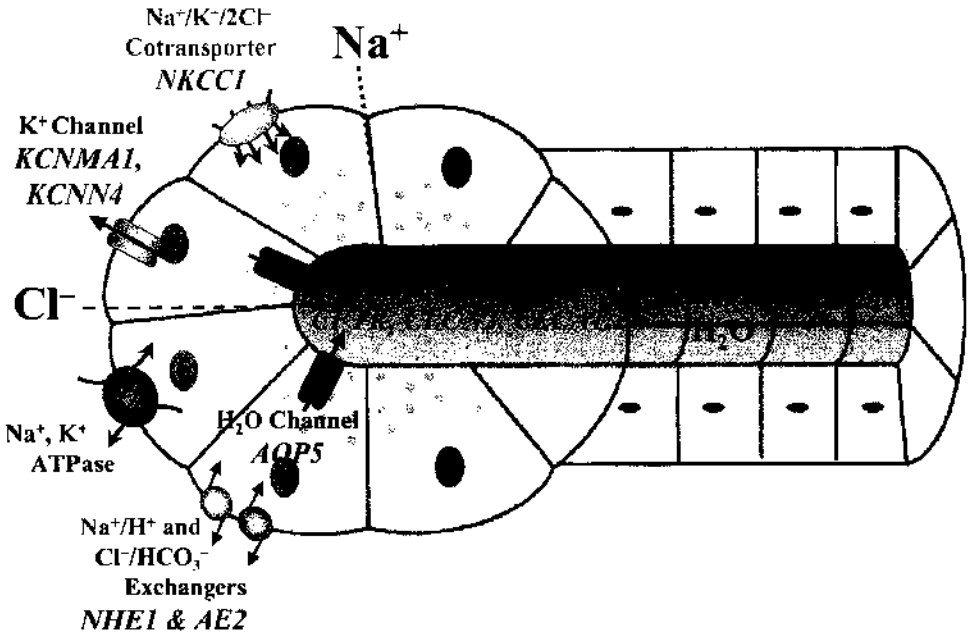


FIGURE 1 Fluid secretion model. Ion transport pathways in a $Cl^-$-secreting acinar cell. Transepithelial $Cl^-$ movement drives the fluid and electrolyte secretion process. This cell shows the seven essential water and ion transport mechanisms involved in fluid and electrolyte movement in Cl -secreting epithelia: the basolateral $Na^+$,$K^+$-ATPase with a stoichiometry of 3 $Na^+$ : 2 $K^+$; the electroneutral $Na^+/K^+/2Cl^-$ cotransporter; the basolateral $K^+$ channel; paired basolateral $Na^+/H^+$ and $Cl^-/HCO_3^-$ exchangers; the apical water channel; and apical $Cl^-$ channels. $Cl^-$ is concentrated in acinar cells by the $Na^+/K^+/2Cl^-$ cotransporter and paired $Na^+/H^+$ and $Cl^-/HCO_3^-$ exchangers. $K^+$ and $Cl^-$ exit when the $K^+$ and $Cl^-$ channel open in response to an increase in the intracellular $[Ca^{2+}]_i$. The accumulation of $Cl^-$ in the acinar lumen is neutralized by $Na^+$ movement across tight junctions and water follows osmotically. See text for details.

basolateral and apical membranes of acinar cells, respectively. A sustained increase in $[Ca^{2+}]_i$, which is dependent on external $Ca^{2+}$, is required to generate a prolonged secretion. Up-regulation of the $Na^+/K^+/2Cl^-$ cotransporter and the $Na^+/H^+$ exchanger by the increase in $[Ca^{2+}]_i$ ensures that the intracellular $Cl^-$ concentration remains above its electrochemical gradient.

$Cl^-$ efflux mediated by the $Ca^{2+}$-activated $Cl^-$ channel is likely the rate-limiting step in the fluid secretion process. Thus, regulation of $Ca^{2+}$-dependent $Cl^-$ channel activity is the key element in the determination of flow rate. An important mechanism regulating this channel is its sensitivity to the intracellular pH. Following muscarinic activation, the intracellular pH of acinar cells typically drops due to $HCO_3^-$ efflux via $Ca^{2+}$-activated $Cl^-$ channels. Channel activation is regulated by pH such that as the intracellular pH decreases, the channel is inhibited. Consequently, $HCO_3^-$ efflux via the $Ca^{2+}$-activated $Cl^-$ channel is blunted and thus the magnitude of the resulting intracellular pH drop is decreased. The importance of the pH sensitivity of the $Ca^{2+}$-activated $Cl^-$ channels is in sustaining fluid secretion during prolonged stimulation. Activation of $Na^+/H^+$ exchange raises the intracellular pH of acinar cells 0.1–0.3 units higher than the pH in unstimulated cells. As the intracellular pH rises, the $Ca^{2+}$ sensitivity of the $Cl^-$ channel increases (and consequently the channel activity increases), evoking continued fluid and electrolyte movement even as the cytosolic $Ca^{2+}$ concentration decreases to near resting levels.

## Molecular Identity of Ion and Water Transport Pathways

Fluid secretion is dependent on the activation of $Ca^{2+}$-gated $Cl^-$ channels. Although four different classes of $Cl^-$ channels have been identified in salivary acinar cells, only one of these is activated by an increase in the intracellular free $Ca^{2+}$ concentration. The molecular identity of the $Ca^{2+}$-activated $Cl^-$ channel is unknown; however, *CLCA1* and *CLCA2*, members of a putative $Ca^{2+}$-gated $Cl^-$ channel gene family, are expressed in salivary glands. Activation of the other three Cl channels is dependent on an increase in cAMP,

hyperpolarization of the plasma membrane, or cell swelling. The cAMP-dependent and the hyperpolarization-activated $Cl^-$ channels are due to the expression of *CFTR* and *CLCN2*, respectively, but the identity of the cell swelling-dependent channel remains unclear. Mutations in functional domains of the *CFTR* gene result in cystic fibrosis, whereas targeted disruption of the *Clcn2* gene leads to degeneration of the retina and testis.

At least two types of $Ca^{2+}$-dependent $K^+$ channels are present in acinar cells, a large-conductance voltage- and $Ca^{2+}$-dependent $K^+$ channel (125–250 pS), the so-called maxi-$K^+$ channel, and an intermediate conductance $Ca^{2+}$-dependent $K^+$ channel (22–35 pS). Evidence suggests that the large-conductance voltage- and $Ca^{2+}$-dependent $K^+$ channel is encoded by *KCNMA1*, whereas the intermediate-conductance $Ca^{2+}$-dependent $K^+$ channel is *KCNN4*. The two $Cl^-$ uptake pathways, the $Na^+/K^+/2Cl^-$ cotransporter and the paired $Cl^-/HCO_3^-$ and $Na^+/H^+$ exchangers, are encoded by the *NKCC1* (*SLC12A2*), *NHE1* (*SLC9A1*), and *AE2* (*SLC4A2*) genes, respectively. Although several different water channel genes are expressed in salivary glands, only the aquaporin *AQP5* has been shown to play a major role in salivation.

## SECRETORY GRANULE DISCHARGE

### Pattern of Innervation versus Signaling of Exocrine Secretion

As described above, both parotid and submandibular acinar elements receive innervation from both branches of the autonomic nervous system. Sympathetic innervation through the activation of β-adrenergic receptors potently stimulates exocrine secretion in these glands mediated by an increase in cAMP and the subsequent activation of PKA. Signaling components downstream of PKA that may function directly in exocrine secretion have been difficult to discern, although a 26 kDa protein phosphorylated by PKA in response to isoproterenol, and having phosphorylation–dephosphorylation kinetics consistent with exocytosis, has been identified in rat parotid and submandibular acinar cells.

Parasympathetic nerves have a much less direct effect on exocrine secretion in these glands. Each of the cotransmitters VIP and acetylcholine may have a positive effect on exocrine secretion, mediated by VIP activation of the cAMP/PKA pathway and acetylcholine stimulation of muscarinic M3 receptors to activate protein kinase C (PKC). PKC consists of three families of isoforms, conventional ($\alpha$, $\beta_I$, $\beta_{II}$, $\gamma$), novel ($\delta$, $\epsilon$, $\eta$, $\theta$), and atypical ($\zeta$, $\lambda/\tau$), that differ in expression, subcellular localization, substrate specificity, and activation mechanisms. In response to muscarinic agonist, acinar cells from rat parotid glands demonstrate activation of both PKCα and PKCδ, whereas submandibular acinar cells undergo stimulation of PKCε but not PKCα. It is still unclear which PKC isoform(s) may be coupled to the exocrine pathways in these cells.

Contrary to parotid and submandibular glands, exocrine secretion as well as fluid secretion by sublingual mucous acinar cells is primarily under the control of muscarinic receptors with activation of both M1 and M3 subtypes required for a maximal exocrine response. The muscarinic exocrine response is totally dependent on activation of a $Ca^{2+}$-dependent PKC isoform(s), of which PKCα is the likely candidate based on expression levels. The function of muscarinic receptor redundancy is unclear. Because minor mucous glands also have a dominant parasympathetic innervation, it is reasonable to speculate that muscarinic receptors also function in a similar manner to stimulate both exocrine and fluid secretion. VIP can also activate exocrine secretion by sublingual mucous cells, but through activation of PKA and to a much lower maximal effect than the muscarinic pathway.

### Pathways for the Sorting and Release of Secretory Proteins

The major regulated pathway for exocrine secretion of salivary proteins/glycoproteins involves the synthesis and transport of proteins/glycoproteins through the ER and Golgi, the budding of condensing vacuoles from the *trans*-Golgi to form immature secretory granules, maturation to secretory granules, and the exocytotic release of granule contents in response to agonist. This pathway functions primarily in the extensive secretion of secretory material during periods of eating. Three additional pathways for the release of secretory proteins have been identified in rat parotid serous acinar cells. Two of these pathways are independent of agonist stimulation; one pathway is associated with the unstimulated exocytosis of mature secretory granules and is apparent after cells are replete with granules. The second unstimulated pathway, the constitutive-like pathway, and a minor regulated pathway are both initiated at a mutual step. This step involves secretory proteins that are sorted inefficiently and enter vesicles that then bud off from both condensing vacuoles and immature secretory granules. Vesicles destined for the constitutive-like vesicles then undergo passage to the apical membrane through recycling endosomes. These endosomes also contain secretory proteins internalized by endocytosis of contents released previously in the apical lumen. During a

4 to 6 h period, from 10 to 15% of newly synthesized secretory proteins are released via the two unstimulated pathways.

Vesicles destined for the minor regulated pathway do not pass through recycling endosomes but instead are sequestered in the apical cytoplasm until induced to release their contents via exocytosis at the apical membrane. This pathway represents a small but significant pool of secretory proteins (up to 10% of newly synthesized amylase) and is responsive to very low doses of either β-adrenergic (≤5 nM isoproterenol) or muscarinic (40 nM carbachol) agonist. In contrast, induction of the major regulated pathway requires higher concentrations of isoproterenol (≥1 μM isoproterenol). The minor regulated pathway may thus contribute more significantly to basal or resting secretions during periods between meals when the parotid receives only low-frequency stimulation from parasympathetic and possibly sympathetic nerves.

Elucidation of distinct pathways for the release of secretory proteins adds additional levels of complexity in efforts to define mechanisms responsible for the differential sorting of vesicles as well as for the control of exocytosis by $Ca^{2+}$- and cAMP-mediated signaling. In other exocrine systems, especially with excitable cells, proteins termed SNARE (soluble *N*-ethylmaleimide-sensitive attachment protein receptor) have been identified and function in a reciprocal recognition between v-SNAREs (vesicular membrane-associated proteins) and t-SNAREs (plasma membrane-associated proteins). Studies with rat parotid acinar cells suggest a role for the v-SNARE protein VAMP2 (vesicle-associated membrane protein 2) in cAMP-mediated exocrine secretion. Also implicated in trafficking of parotid vesicles are the small GTP-binding proteins Rab3, Rap1, and ARF1 (ADP-ribosylation factor 1) as well as SCAMP1 (secretory carrier membrane protein 1). Moreover, the recent demonstrated expression in parotid glands of additional SNAREs as well as associated regulatory proteins known to function in membrane fusion events further manifests the complexity of defining the key downstream events regulating salivary exocrine secretion.

## INTERACTIONS BETWEEN SECRETORY STIMULI

### Crosstalk between Signaling Pathways

Glandular elements normally receive multiple signals, either from co-localized neurotransmitters or from the simultaneous firing of both sympathetic and parasympathetic fibers (at least in parotid and submandibular glands). In general, synergistic fluid and exocrine effects are observed in response to mixed low-level nerve stimulation in parotid and submandibular glands. Mechanisms of synergistic interactions may involve contributions from myoepithelial cells, augmentation of calcium or cAMP signaling by different receptors, or convergence of two distinct pathways at a common secretory mechanism. For example, norepinephrine from sympathetic nerves is likely to stimulate a maximal exocrine response from serous cells as both the cAMP and $Ca^{2+}$ pathways are activated via β- and $\alpha_1$-adrenergic receptors, respectively. Moreover, $\alpha_1$-adenergic receptors mediate the small sympathetic-derived fluid component of norepinephrine-induced secretion. In mouse parotid acini, the observed synergism between the muscarinic and β-adrenergic pathways in fluid and exocrine secretion is likely related to (1) $Ca^{2+}$ activation of calmodulin (CaM) with subsequent CaM stimulation of the type 8 isoform of adenylyl cyclase and (2) cAMP potentiation of $Ca^{2+}$ release from intracellular stores due to PKA-mediated phosphorylation of $IP_3$ receptors. In addition, a functional $Ca^{2+}$–nitric oxide–cGMP pathway in acinar cells may also serve to integrate $Ca^{2+}$ and cAMP levels through actions to promote or amplify increased $[Ca^{2+}]_i$ and inhibit adenylyl cyclase isoforms.

### See Also the Following Articles

**Autonomic Innervation • Salivary Glands, Anatomy and Histology • Sjögrens Syndrome • Substance P • Taste and Smell • Vasoactive Intestinal Peptide (VIP) • Xerostomia**

### Further Reading


Ahn, J. S., Camden, J. M., Schrader, A. M., Redman, R. S., and Turner, J. T. (2000). Reversible regulation of $P2Y_2$ nucleotide receptor expression in the duct-ligated rat submandibular gland. *Am. J. Physiol. Cell Physiol.* 279, C286–C294.

Ambudkar, I. S. (2000). Regulation of calcium in salivary gland secretion. *Crit. Rev. Oral Biol. Med.* 11, 4–25.

Begenisich, T., and Melvin, J. E. (1998). Regulation of chloride channels in secretory epithelia. *J. Membr. Biol.* 163, 77–85.

Bockman, C. S., Bradley, M. E., Dang, H. K., Zeng, W., Scofield, M. A., and Dowd, F. J. (2001). Molecular and pharmacological characterization of muscarinic receptor subtypes in a rat parotid gland cell line: Comparison with native parotid gland. *J. Pharmacol. Exp. Ther.* 297, 718–726.

Bruce, J. I., Shuttleworth, T. J., Giovannucci, D. R., and Yule, D. I. (2002). Phosphorylation of inositol 1,4,5-trisphosphate receptors in parotid acinar cells. *J. Biol. Chem.* 277, 1340–1348.

Cook, D. I., Van Lennep, E. W., Roberts, M. L., and Young, J. A. (1994). Secretion by the major salivary glands. *In* "Physiology of the Gastrointestinal Tract" (L. R. Johnson, ed.), 3rd Ed., pp. 1061–1117. Raven Press, New York.

Culp, D. J., Luo, W., Richardson, L. A., Watson, G. E., and Latchney, L. R. (1996). Both M1 and M3 receptors regulate exocrine secretion by mucous acini. *Am. J. Physiol.* 271, C1963–C1972.

Dowd, F. J. (1999). Saliva and dental caries. *Dent. Clin. North Am.* 43, 579–597.

Garrett, J. R. (1987). Innervation of salivary glands: Neurohistological and functional aspects. *In* "The Salivary System" (L. M. Sreebny, ed.), pp. 69–93. CRC Press, Boca Raton, FL.

Huang, A. Y., Castle, A. M., Hinton, B. T., and Castle, J. D. (2001). Resting (basal) secretion of proteins is provided by the minor regulated and constitutive-like pathways and not granule exocytosis in parotid acinar cells. *J. Biol. Chem.* 276, 22296–22306.

Lundberg, J. M., Martling, C.-R., and Hökfelt, T. (1988). Airways, oral cavity and salivary glands: Classical transmitters and peptides in sensory and autonomic motor neurons. *In* "Handbook of Chemical Neuroanatomy, Vol. 6, The Peripheral Nervous System" (A. Björklund, T. Hökfelt, and C. Owman, eds.), pp. 391–444. Elsevier Science, Amsterdam.

Melvin, J. E. (1991). Saliva and dental diseases. *Curr. Opin. Dent.* 1, 795–801.

Nauntofte, B. (1992). Regulation of electrolyte and fluid secretion in salivary acinar cells. *Am. J. Physiol.* 263, G823–G837.

Quissell, D. O., Watson, E., and Dowd, F. J. (1992). Signal transduction mechanisms involved in salivary gland regulated exocytosis. *Crit. Rev. Oral Biol. Med.* 3, 83–107.

Turner, R. J., Paulais, M., Manganel, M., Lee, S. I., Moran, A., and Melvin, J. E. (1993). Ion and water transport mechanisms in salivary glands. *Crit. Rev. Oral Biol. Med.* 4, 399–406.

# *Salmonella*

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nuclear factor κB Conserved signal transduction pathway critical for the activation of innate immune and inflammatory responses.

Toll-like receptors Transmembrane surface receptors involved in the detection and recognition of pathogen structural determinants.

**The *Salmonella*, a large group of common bacterial enteric pathogens, cause a spectrum of food-borne and waterborne diseases of worldwide importance. Generally, clinical syndromes are divided into nontyphoidal salmonellosis and typhoid fever. Nontyphoidal salmonellosis is an acute inflammatory gastroenteritis of great public health importance in industrialized countries and is caused by many *Salmonella* strains. Typhoid fever, a more severe systemic waterborne disease endemic in developing nations, is caused by a single serovar, *Salmonella typhi*.**

## MICROBIOLOGY

The *Salmonella* are gram-negative, facultative anaerobic, noncapsulated (except *S. typhi/paratyphi*), nonspore-forming, motile rods. They possess a 4.8 Mb genome, variably modified by multiple lysogenic phage genomes, plasmids, and other mobile genetic elements. Interestingly, the *S. typhi* genome contains numerous inactive pseudogenes, which are functional in enteropathogenic *Salmonella* strains. *Salmonella* taxonomy is complex and in a constant state of revision. All *Salmonella* are members of the family Enterobacteriaceae and are closely related to other medically important enteric bacteria including *Escherichia coli*, *Yersinia* sp., and *Shigella* sp.

By DNA sequence analysis, six subgroups of "*Salmonella enterica*" are recognized. Almost all human (and other warm-blooded animal) pathogens, including *S. typhi*, are in Group 1. Group 1 is further categorized into more than 1000 serovars based on the antigenicity of surface oligosaccharides (O-antigens) and flagellar structures (H-antigens). Roughly 10 Group 1 serovars account for over 70% of human infections. Other subgroups of *Salmonella* are found primarily in cold-blooded animals and the environment, though several serovars of Group 3 can occasionally be pathogenic in humans. In the medical and epidemiological literature, isolates are generally referred to by serovar elevated to species name.

All *Salmonella* are adapted to the intestinal tracts of vertebrates. Some can colonize/infect a broad range of vertebrate hosts; alternatively, strains may have absolute host specificity. *S. typhi*, for example, is strictly host limited to humans. Certain *Salmonella* strains can

be effective intestinal commensals in birds and reptiles and can also colonize reproductive organs. This ability allows infection of developing eggs and subsequent vertical transmission, which accounts for human infection via the poultry industry and pet trade. *Salmonella* are hardy organisms and can survive under a variety of environmental conditions outside a vertebrate host. For instance, infective organisms can survive in soil for months and in dried food products for years.

## CLINICAL SYNDROMES

Nontyphoidal salmonellosis is caused by many *Salmonella* serovars and is generally manifested as an acute inflammatory gastroenteritis. Symptoms usually begin after an incubation period of 1–4 days with initial nausea and vomiting followed by cramping abdominal pain, diarrhea, headache, and fever. The illness generally lasts 3–7 days and is usually self-limited. Mortality is rare and is usually confined to elderly and immunocompromised patients, such as individuals with acquired immunodeficiency syndrome or neoplastic disease. The diarrhea is usually of moderate volume and without blood. Frankly bloody and purulent "dysentery-like" stools can be seen, though such symptoms are more typical of *Shigella* or enterohemorrhagic *E. coli* infections. In addition, voluminous watery "cholera-like" stools occur occasionally in nontyphoidal salmonellosis. Rarely, an enteric fever-like clinical picture can result from infection with nontyphoidal *Salmonella*.

The diagnosis of nontyphoidal salmonellosis should be considered in any enterocolitis, especially when associated with fever and headache. Definitive diagnosis is achieved by stool culture on selective medium to rule out other enteropathogens, such as *Campylobacter* sp., *Shigella*, *Yersinia*, or pathogenic *E. coli*, and to differentiate from acute idiopathic ulcerative colitis or toxigenic secretory diarrhea.

Complications include bacteremia and subsequent localized extraintestinal infections, e.g., arthritis, meningitis, osteomyelitis (especially in patients with sickle cell anemia), and endocarditis. Such bacteremic complications are often associated with certain serovars (e.g., *S. choleraesuis* and *S. dublin*) or in the clinical setting of immunodeficiency or hemolytic disorders. Autoimmune sequelae such as Reiter syndrome (joint pain, uveitis, and urethritis) can follow *Salmonella* (and other enteric) infections, generally in HLA-B27-positive males.

Pathological change is limited to the colon and ileum and is marked by mucosal erosions with a variable inflammatory infiltrate in the epithelia and lamina propria. In acute infections, neutrophilic infiltration of the epithelia and lumen is characteristic. The histopathologic picture may be mistaken for acute ulcerative colitis.

Typhoid or enteric fever is caused by *S. typhi* and is a severe systemic febrile infection that involves the reticuloendothelial system. Paratyphoid fever is a similar slightly milder syndrome caused by the closely related *S. paratyphi*. After oral inoculation and an incubation period of 8–14 days, patients present with variable gastrointestinal symptoms (generally milder than those in nontyphoidal salmonellosis), prolonged high fever, constipation, headache, and incapacitating malaise. A characteristic maculopapular rash (rose spots) may be seen and hepatosplenomegaly is common. Untreated, the clinical course is 3–8 weeks, with convalescence (and possible relapse) often extending much longer, resulting in mortality from chronic inanition. Overall, the mortality rate of untreated infection is 10–20%.

Definitive diagnosis is made by culture (the highest yield is obtained from bone marrow; otherwise blood, duodenal fluid, or skin is taken). Pathology is characterized by expansion of the macrophage-like cells in reticuloendothelial and lymphoid tissues, accounting for the hepatosplenomegaly. Massive enlargement, necrosis, and rupture of mucosal Peyer's patches can result in gut perforation, a feared often-lethal complication. As in nontyphoidal salmonellosis, disseminated infection can occur.

## EPIDEMIOLOGY

Nontyphoidal salmonellosis is rising in incidence in industrialized nations, with 2–4 million documented cases per year and far more going unreported. The predominant (90%) route of infection is food-borne, especially through beef and poultry products. Person-to-person transmission occurs, such as in day-care centers, but is less common. Infections peak in the summer and fall months and most cases are sporadic, though recognized outbreaks are well known and can often be traced to a common source. Although all ages can be affected, young children and the elderly are diagnosed far more frequently. Immunization is not effective in nontyphoidal salmonellosis and individuals can suffer repeated infections.

Typhoid fever is uncommon in industrialized nations (several hundred cases annually in the United States since the mid-1960s, largely confined to travelers and laboratory workers) but remains a serious issue in the developing world. The World Health Organization

estimates 33 million cases annually worldwide, with >500,000 deaths. As humans are the only host of this organism, the disease is spread in an indirect person-to-person fashion, generally through fecally contaminated water supplies, and thus is endemic in areas with limited sanitation. In developed nations with efficient water purification and sewage disposal capabilities, typhoid fever is rare. Endemic areas tend to be large impoverished urban areas in Central America, South America, South Asia, and Southeast Asia.

In striking contrast to *Salmonella* enteritis, typhoid fever predominantly strikes older children and young adults, with fewer infections in the very young and old. Interestingly, pretechnical societies have a low incidence of infection, probably due to universal exposure during the relatively protected period of infancy, resulting in population immunity.

Typhoid fever confers immunity to subsequent attacks; however, *S. typhi* has a predilection for colonizing the gallbladder and can remain in high numbers even after the patient has clinically recovered. Such chronic carrier individuals (2–5% of cases) continually shed large numbers of organisms into the bile and intestinal tract, presenting a public health challenge. The case of "Typhoid Mary," a 19th century New York cook deemed responsible for over 3000 infections, vividly illustrates the potential for person-to-person transmission from chronic carriers.

## PATHOGENESIS

All *Salmonella* are enteric pathogens and are transmitted orally via contaminated food and water. Thus, all enteropathogens must survive transit through the acidic gastric environment to gain access to the distal ileum and colon, affix themselves to the lumenal wall to avoid peristaltic elimination, and engage the host at the intestinal epithelium.

*Salmonella* are invasive organisms; events leading to disease are elicited by the actual penetration of the epithelial barrier by living organisms. This is in contrast to other enteridites mediated by the action of extracellular secreted toxins, such as in cholera or staphylococcal-mediated food poisoning. It is generally accepted that the process of invasion is mediated by bacterial "effector" proteins injected into the cytoplasm of the host cell by means of a specialized secretory structure (type III secretion system, or TTSS). The TTSS is found in many gram-negative pathogens and its component structural and regulatory genes tend to be physically clustered on "pathogenicity islands" (PAIs). Effector proteins may be encoded in pathogenicity islands either contiguous with TTSS proteins or elsewhere on the chromosome. Effector proteins are thought to usurp host cellular processes to facilitate the bacterial life cycle. The PAI of *Salmonella* shows significant homology with the PAIs of other enteropathogens, in both gene order and gene sequence, suggesting that these determinants of virulence have been disseminated among enteric organisms by horizontal gene transfer. The presence of virulence factors on other mobile genetic elements, such as temperate phage DNA and plasmids, further supports the idea of horizontal transmission of genes involved in pathogenicity.

Translocated effector proteins can induce phagocytosis into intestinal epithelial cells, allowing penetration of the epithelial barrier, occupation of an intracytoplasmic vacuole, and egress through the basolateral aspect of the epithelium into the lamina propria. In addition, lumenal *Salmonella* may be taken up by M cells, which are modified epithelial cells overlying lymphoid tissue that are specialized to sample lumenal particulate matter, and thus gain access to the lamina propria in this manner.

In nontyphoidal salmonellosis, the presence of invading bacteria is detected by the innate immune system, most likely via perception of bacterial surface structures by Toll-like receptors. The subsequent elicitation of the nuclear factor κB and other pro-inflammatory cellular signaling pathways results in activation of a classical acute inflammatory response typified by an intense neutrophilic infiltrate present in the mucosa, submucosa, and lumen. This cellular infiltrate and the resultant increased epithelial permeability directly contribute to the clinical manifestations of the disorder, namely, inflammatory and secretory diarrhea. *Salmonella* are rapidly killed by neutrophils. Thus, the brisk inflammatory response, despite the clinical symptoms it induces, localizes the infection and arrests systemic dissemination.

In typhoid fever, *S. typhi* and *S. paratyphi* are able to adhere, invade, and penetrate the mucosa without eliciting a significant inflammatory response. This property may be mediated by the polysaccharide capsule specific to these serovars. Organisms are phagocytosed by recruited macrophages and ultimately reach and proliferate within the monocytic cells of the reticuloendothelial system, with resultant enlargement of lymph nodes and spleen. These cells are apparently unable to kill *S. typhi*, resulting in protection of the pathogen from host innate and adaptive immunity. The prolonged fever and malaise associated with typhoid fever are likely a reaction to circulating bacterial products and endogenous cytokines produced

chronically from the massive persistent systemic infection.

## TREATMENT AND PREVENTION

Nontyphoidal salmonellosis is a self-limited disease in immunocompetent adults. Antimicrobial administration does not reduce symptom severity or duration; indeed, antibiotics prolong asymptomatic passage of organisms during convalescence, presumably due to effects on normal flora that otherwise suppress growth of pathogens. In cases of *Salmonella* bacteremia or extraintestinal infection, quinolones, trimethoprim-sulfamethoxazole, and amoxicillin are generally indicated. Passive immunization against intestinal salmonellosis is not available.

The most effective control mechanisms are directed toward the source of infections. Improved methods of animal husbandry, meat processing, and storage are effective in reducing outbreaks. Hand-washing among workers in day care and other institutional settings and education of individuals about proper food-handling practices and preparation techniques at the commercial and household level are also important.

Typhoid fever generally responds to chloramphenicol, quinolones, and trimethoprim-sulfamethoxazole, though the emergence of multidrug-resistant strains is an ominous problem. In the case of chronic carriers, *S. typhi* can be successfully eradicated by prolonged antimicrobial therapy, underscoring the importance of identifying and treating these individuals. As typhoid is waterborne, efforts in developing countries to guard the purity of water sources and safely process sewage are considered primary methods of control. Reasonably effective vaccines are available and are often used by travelers to endemic areas.

With all forms of *Salmonella*-mediated diseases, domestic and international epidemiological surveillance is necessary to detect outbreaks and identify carriers. Unfortunately, the severity of typhoid fever and environmental hardiness of *S. typhi* could lead to deliberate contamination of water supplies, further emphasizing the need to monitor this disease.

### See Also the Following Articles

**Cholera • Foodborne Diseases • Food Poisoning • Food Safety • Gastroenteritis • *Shigella* • *Yersinia***

### Further Reading

Hornick R. (1994). Nontyphoidal salmonelloses. *In* "Infectious Diseases" (P. Hoeprich, M. Jordan, and A. Ronald, eds.), 5th Ed., pp. 741–747. Lippincott, Philadelphia, PA.

Hornick R. (1994). Typhoid fever. *In* "Infectious Diseases" (P. Hoeprich, M. Jordan, and A. Ronald, eds.), 5th Ed., pp. 747–753. Lippincott, Philadelphia, PA.

Levine, M. (1998). Typhoid fever. *In* "Bacterial Infections of Humans: Epidemiology and Control" (A. Evans and P. Brachman, eds.), 3rd Ed., pp. 839–858. Plenum, New York.

Pegues, D., Ohl, M., and Miller, S. (2002). *Salmonella*, including *Salmonella typhi*. *In* "Infections of the Gastrointestinal Tract" (M. Blaser, P. Smith, J. Ravdin, H. Greenberg, and R. Guerrant, eds.), 2nd Ed., pp. 669–697. Lippincott Williams & Wilkins, Philadelphia, PA.

Tauxe, R., and Pavia, A. (1998). Salmonellosis: Nontyphoidal. *In* "Bacterial Infections of Humans: Epidemiology and Control" (A. Evans and P. Brachman, eds.), 3rd Ed., pp. 613–630. Plenum, New York.

# Satiety

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**anabolic pathway/signal** Neural circuit/input promoting food intake.

**blood–brain barrier** Specific configuration of the endothelial cells of the brain blood vessels that does not allow the passage of molecules; only molecules using energy-requiring transport mechanisms can cross this barrier.

**catabolic pathway/signal** Neural circuit/input reducing food intake.

**circumventricular organs** Brain area where blood vessels are not equipped with the blood–brain barrier, thus allowing the entry of small peptides into the brain.

**hypothalamus** Integrative brain area made up of different nuclei; it receives inputs from the periphery and triggers the appropriate behavioral and biochemical responses.

**neuropeptide** A short chain of amino acids acting as a neurotransmitter.

**neurotransmitter** A molecule transferring information between neurons.

**peptide** A short chain of amino acids.

**vagus nerve/vagal afferents** The parasympathetic component of the autonomic nervous system, conveying metabolic and mechanical information from the periphery to the hypothalamus.

**To sustain life and growth, satiety is a critical feeling whose function is to avoid overfeeding. As a consequence, the biological mechanisms regulating the onset of satiety are closely interconnected with those regulating the onset of appetite and ultimately they both control food intake. This article will discuss the currently accepted model of the regulation of food intake, by detailing the peripheral inputs that are conveyed to the brain, which in turn integrates this information and triggers the appropriate behavioral response.**

## SATIETY AND APPETITE AS REGULATORS OF FOOD INTAKE

In everyday parlance, the words life and energy are often used as synonyms. This common use sounds scientific, because a close biological relationship exists between these two concepts since growth, metabolic processes, physical activity, and reproduction would be impossible without energy. Thus, the ability to maximize the balance between energy expenditure and energy intake represents the primary factor in promoting the survival and evolution of a species. Less efficient processes would ensure the progressive disappearance of a species.

One of the most fascinating biological characteristics of humans is the ability to closely match energy intake with energy expenditure, which should prevent the onset of morbid obesity or malnutrition. This extraordinary level of precision can be illustrated by a few calculations. Over the course of a decade, the weight of an average adult tends to increase slightly whereas over the same period, approximately 10 million kilocalories are consumed. To account for the modest change in weight that is generally observed, energy intake must closely match energy expenditure within 0.17% per decade. An efficient regulatory system must therefore exist.

Behaviorally, energy intake is regulated by a simple mechanism, involving the cyclical occurrence of specific feeling-associated stimuli informing the individual when a meal should be initiated and when it should be stopped. Two anabolic stimuli regulate the start of a meal, each indicating a specific need: hunger, which represents a metabolic feeling since it expresses a general need for calories; and appetite, which results mainly from cognitive inputs because it expresses the need for a specific food and is thus related to the palatability of food, its texture, and one's previous experience regarding that particular food. Similarly, two catabolic stimuli control when a meal should be stopped: satiation, representing a "physical" feeling since it expresses the feeling of abdominal fullness that stops a meal; and satiety, a primarily metabolic feeling since it expresses the interprandial lack of any desire to start a new meal. These basic feeling-related stimuli are controlled and regulated by a very complex network, whose integrating center is located in the brain and principally in the hypothalamus. In health and disease, the control of food intake is based on a complex series of biochemical interactions between the brain and the peripheral organs, usually leading to appropriate food intake

 

behavioral responses. Indeed, the currently accepted model for the control of energy intake postulates that energy intake is modulated mainly within the hypothalamus. This continuously regulates the energy status of the body by directly sensing the presence of nutrients in the bloodstream and by receiving afferent input from the periphery (oronasal, gut, liver, adipose tissue). Also, monoamines, neuropeptides, and cytokines produced in the brain and the gastrointestinal (GI) tract during a meal can directly or indirectly activate vagal afferents and mediate many of the nutrients' effects on appetite, gut functions, anabolism, and catabolism. In the hypothalamus, specific neuronal populations transduce these inputs into neuronal responses and, via second-order neuronal signaling pathways and efferent output, into behavioral responses.

## PERIPHERAL SIGNALS INFLUENCING SATIETY

To closely regulate the cyclical recurrence of hunger and satiety, the hypothalamus needs to be continuously informed about adipose tissue status, the activity of the GI tract, and the metabolic status of peripheral tissues. To this end, a number of peripheral signals have evolved to assist in maintaining the homeostasis of energy intake (Fig. 1).

### Adiposity Signals

Two main adiposity signals exists, leptin and insulin. Leptin is produced primarily by adipocytes and insulin is secreted by the endocrine pancreas. Plasma concentrations of leptin and insulin are proportionate to body fat mass. Both hormones enter the brain via specific receptors located on the blood–brain barrier. Among them, leptin appears to exert a greater influence on energy intake and a rise in its circulating levels results in inhibition of energy intake and increasing energy expenditure. Similarly, insulin enters the brain from the circulation and acts to reduce energy intake. Leptin and insulin receptors are expressed by brain neurons involved in energy intake. Administration of either peptide directly into the brain reduces food intake, whereas their antagonists or a deficiency of either hormone has the opposite effect. Leptin and insulin act on central effector pathways in the hypothalamus, activating catabolic circuits that inhibit food intake and increase energy expenditure, while simultaneously silencing brain anabolic neural circuits that stimulate eating and inhibit energy expenditure. Conversely, low leptin and insulin concentrations in the brain, which occur during weight loss, stimulate the activity of anabolic neural pathways that enhance eating and suppress energy expenditure; low concentrations of leptin and insulin also inhibit the activity of catabolic pathways that cause anorexia and weight loss.

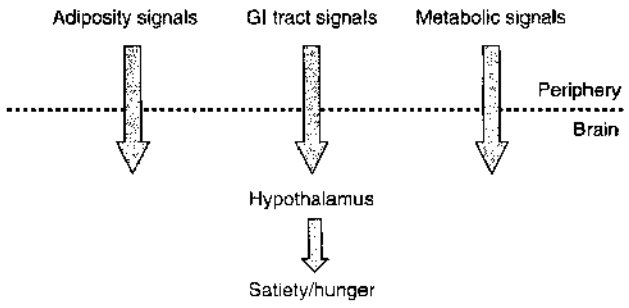


FIGURE 1 Mechanisms controlling food intake. The hypothalamus integrates a large number of inputs relaying to the center the comprehensive status of peripheral tissues. Based on the analysis of these biochemical, mechanical, and metabolic signals, the hypothalamus triggers the appropriate behavioral response, being either the onset of satiety, thus stopping a meal, or the onset of hunger, thus initiating a new meal.

### GI Tract Signals

The GI tract produces a number of peptides in response to feeding and fasting, which act directly in the hypothalamus. Among these, the most important are ghrelin and cholecystokinin (CCK).

#### *Ghrelin*

Ghrelin is a peptide/neuropeptide released from the stomach in response to fasting and stimulates food intake. It is a ligand for the growth hormone secretagogue (GHS) receptor and when purified has 28 amino acids. Ghrelin and its mRNA as well as the GHS receptors are expressed in the hypothalamus. Both peripheral and central administration of ghrelin stimulated food intake and increased body weight in freely feeding rodents. Ghrelin concentrations in blood and its mRNA in stomach increase by fasting and decrease by refeeding and after Roux-en-Y gastric bypass surgery. The ingestion of sugar, but not gastric distension, decreases circulating ghrelin concentrations. These data suggest that the presence of endogenous ghrelin stimulates the hypothalamus, indicating that ghrelin is the first appetite stimulatory peptide produced by the oxyntic cells of the stomach that act as a neuropeptide in the hypothalamus.

#### *Cholecystokinin*

Cholecystokinin is an important signal involved in the regulation of food intake. It is a satiety signal that

acts as a paracrine substance to stimulate pancreatic secretion via vagal cholinergic fibers, but it also reaches the brain to exert its catabolic effect. In addition, CCK sensitizes vagal afferents to mechanical stimuli (e.g., gastric distension) and potentiates the effects of mechanical stimulation on meal termination. Indeed, the mechanical distension of abdominal walls, in particular the gastric wall, is a potent satiety signal that is promptly relayed to the brain via neural afferents. Also, the presence of nutrients in the intestine inhibits eating and gastric emptying.

### *Peptide $YY_{3-36}$*

The hormone $PYY_{3-36}$ is secreted by endocrine cells lining the distal small bowel and colon in response to food. Its concentrations in the blood remain elevated between meals and thus it suppresses interprandial appetite. It is a member of the neuropeptide Y (NPY) family, acting in the arcuate nucleus of the hypothalamus, where it binds specifically to the Y2 receptor. It modulates the NPY/Agouti-related peptide complex (see below).

## Metabolic Signals

The onset of satiety is controlled not only by the extension of adipose tissue and by the presence of food within the GI tract but by the metabolic status of the body and the circulating levels of some nutrients.

### *Energy Signals*

Like changes in fat mass, changes in hepatic energy metabolism influence energy intake in a leptin-independent manner via energy signals relayed to the brain via vagal afferents. A number of studies suggest that a metabolic control of food intake also exists, in which the biochemical partitioning between fatty acid oxidation and synthesis represents a key signal indicating catabolic or anabolic energy status. Although apparently similar, adiposity signals (i.e., leptin and insulin) and energy signals are different and specific. Adiposity signals act as an adipostat and inform the brain about the extension of body fat mass. Energy signals are independent of the leptin pathway and thus independent of body mass extent, but they inform the brain about the metabolic switch occurring at a subcellular level between fatty acid oxidation and synthesis. Further evidence for the involvement of energy signals in the control of energy intake has recently been provided by findings showing that systemic and intracerebroventricular treatment of mice with fatty acid synthase inhibitors leads to inhibition of feeding and weight loss. More specifically, it appears that fatty acids are not the signal determining the cessation of energy intake but rather the intracellular levels of malonylcoenzyme A: its intracellular accumulation inhibits energy intake and its depletion restores energy intake. Fatty acid synthase inhibitors inhibit the expression of the prophagic signal NPY in the hypothalamus, acting in a leptin-independent manner.

### *Nutrient-Related Signals*

Glucose-sensitive cells are present in the endocrine pancreas, liver, and duodenum and are innervated by vagal afferents projecting via the vagus to the nucleus of the solitary tract (NTS). Neurons receptive to concentrations of glucose and other nutrients are present in several regions of the central autonomic network. Central glucose receptors respond to other metabolites (e.g., free fatty acids) as well as changes in concentrations of insulin and glucagon. Glucose concentrations probably alter neuronal firing via ATP-sensitive potassium ion channels similar to those present in the pancreas.

The macronutrient composition of the diet may also promote the onset of satiety by modulating brain monoamines in the hypothalamic sites involved in food intake regulation, based on the competitive uptake of free tryptophan (Trp) with other large neutral amino acids, particularly the branched-chain amino acids. Animals consuming a high-carbohydrate compared to a low-carbohydrate and high-protein diet show increased concentrations of circulating Trp or tyrosine (Tyr). The monoamines include dopamine (DA) and serotonin (5-HT), and the catecholamines norepinephrine (NE) and epinephrine (E). DA and NE are synthesized from Tyr and 5-HT is derived from Trp. The rate at which they synthesize their neurotransmitters is influenced by the precursor amino acid concentration available to the neuron and is controlled by an enzyme that is only partly saturated with substrate at normal brain amino acid concentrations. Therefore, the increase or decrease in concentration of Trp or Tyr can influence the synthesis of 5-HT or DA and NE, respectively. A high-carbohydrate diet promotes the uptake of Trp into the brain and its subsequent conversion to 5-HT, which then terminates the meal and induces satiety. Carbohydrates terminate a meal in two ways, either via a direct effect on 5-HT synthesis or in conjunction with insulin, which also affects 5-HT and its metabolite. However, it must be emphasized that under physiological conditions, several neurotransmitters are involved in food intake initiation and termination. As an example, DA regulates hunger and satiety by acting on corresponding reciprocal hypothalamic areas: DA in

the lateral hypothalamic area (LHA) has a positive stimulatory effect on food intake by modulating the size of a meal via changing gastric compliance, whereas DA in the ventromedial hypothalamus (VMH) inhibits LHA activity. On the other hand, increased intra-LHA and decreased-VMH serotonin levels are associated with the regulation of food intake. These monoamines function in close conjunction with the stimulatory and inhibitory neuropeptides. Thus, the central catabolic initiators interact with numerous factors: psychological and physiological factors, peripheral and central factors, as well as monoaminergic and peptidergic factors.

## HYPOTHALAMIC INTEGRATION OF PERIPHERAL SIGNALS

As previously noted, the hypothalamus plays a major role in the sequence of chemical, autonomic, and endocrine events regulating food intake and metabolism. Not only does the hypothalamus contain glucose-sensitive neurons, it also is extensively vascularized and receives hormones including gastrointestinal peptides via the circumventricular organ. The hypothalamus receives viscero-sensory inputs from vagal afferents, via a relay in the NTS and ventrolateral medulla. Connections of the hypothalamus with the limbic cortex, amygdala, and nucleus accumbens allow integration of peripheral information with various cognitive and emotional factors related to memory of the degree of pleasure associated with food. Its autonomic outputs are important for the control of intermediary metabolism, including the concentrations of blood glucose, free fatty acids, and amino acids as well as the regulation of the endocrine pancreas.

Under normal conditions, peripheral signals (adiposity signals, GI tract signals, and metabolic signals) reach the hypothalamus and directly or indirectly interact with two separate neuronal populations: the NPY/Agouti-related peptide (AgRP) neurons and the proopiomelanocortin (POMC) neurons. These neurons constitute two pathways, the former stimulating and the latter inhibiting energy intake. As a consequence, when energy intake needs to be initiated, peripheral signals activate the NPY/AgRP pathway, simultaneously inhibiting the POMC pathway. When energy intake needs to be inhibited, the rise in peripheral signals inhibits the NPY/AgRP pathway while simultaneously activating POMC neurons and thus up-regulating the expression of a number of POMC pathway-related factors, including α-melanocyte-stimulating hormone (α-MSH), corticotropin-releasing factor (CRF), and cocaine- and amphetamine-related transcript (CART). These catabolic and anabolic effector systems constitute a series of discrete neurotransmitter systems and axonal pathways in the brain, which are concentrated in the arcuate nucleus (ARC) in the ventral hypothalamus.

### Neuropeptide Y

Among the best-described anabolic effector peptides is NPY, a 36-amino-acid peptide. Although the NPY mRNA and the peptide are distributed throughout the central nervous system with a particularly high concentration in the hypothalamus, NPY-containing cell bodies in the ARC are especially important in the control of energy homeostasis. Administration of exogenous NPY into the cerebral ventricle elicits a rapid increase in food intake and a decrease in energy expenditure. Repeated central administration of NPY leads readily to obesity. Inhibition of endogenous NPY synthesis in the ARC by antisense oligonucleotides reduces food intake and body weight.

### Melanocortins

The catabolic effector system POMC also resides within the ARC. Melanocortins (MCs) have the opposite effect as NPY. Melanocortins constitute a family of peptides including ACTH, α-MSH, and CART and represent a growing list of peptides that promote negative energy balance. Neuronal synthesis of these peptides increases in response to increased adiposity signaling in the brain. Among these, the MC system is an important catabolic effector system due to its complexity in energy homeostasis. MCs are cleaved from the POMC, a precursor molecule, and exert their effects by binding to members of a family of MC receptors. Two MC receptors, MC3 and MC4, have been identified within the hypothalamus and are involved in the control of energy homeostasis. Administration of α-MSH and other MC receptor agonists into the third ventricle reduces food intake and body weight, whereas MC receptor antagonists (such as SHU-9119) increase food intake and body weight. In addition, the MC system is important in mediating the effects of leptin, which stimulates POMC mRNA. POMC gene expression is reduced in negative energy balance and is concomitantly increased in positive energy balance. Moreover, the MC receptor antagonist blocks the effect of leptin in reducing food intake. These hypothalamic control systems suggest that the endogenous POMC/α-MSH/MC receptors are a key catabolic effector pathway capable of regulating the effects on food intake and body weight that mediate the effect of adiposity signals in the CNS.

## SECOND-ORDER NEURONAL SIGNALING PATHWAYS

NPY/AgRP and POMC neurons largely project to other hypothalamic areas, including the paraventricular nucleus (PVN), LHA, and VMH, interacting with a number of neuronal populations. These hypothalamic areas are involved in the regulation of food intake and energy expenditure via efferent pathways, including the control of sympathetic and parasympathetic outputs to the endocrine pancreas and the adrenal gland. These pathways act as the final "effector" mechanism controlling food intake and intermediary metabolism.

The PVN is the site of integration and interaction of multiple influences affecting GI function and food intake. Stimulation of the PVN influences gastric motility and secretion via its connections with the dorsomedial hypothalamic nucleus. Circulating glucocorticoids potentiate norepinephrine, which acts on the PVN to stimulate carbohydrate intake. As described above, carbohydrate intake stimulates the production of 5-HT and is inhibited by 5-HT receptors, thereby explaining the anorexic effect of 5-HT and the orexigenic effect of 5-HT antagonists. The PVN is also the main site where other peptides, including opioids, act to increase the ingestion of fat, which is attenuated by DA. This explains both the anti-orexigenic effects of dopamine-releasing drugs such as amphetamine and the increase of fat intake and body weight gain observed as a side effect of treatment with dopamine receptor-blocking neuroleptics.

Many pathways serving as second-order neuronal signaling pathways, which are important mediators in the energy homeostasis process, have been described. They are also intimately linked with monoaminergic coreceptors, suggesting their combined role in the process of catabolism and anabolism. For example, the PVN has neurons that synthesize CRF, thyrotropin-releasing hormone, and oxytocin and their administration causes a net catabolic effect. On the other hand, the LHA synthesizes melanocyte-concentrating hormone and the orexins and the administration of these neuropeptides into the central nervous system causes a net anabolic response.

### Corticotropin-Releasing Factor

Corticotropin-releasing factor, a 41-amino-acid peptide, is a mediator of endocrine, autonomic, and immune responses in stress, and activation of the CRF system is suggested to induce stress-related responses including anorexia and anxiety-like behaviors. Two subtypes of CRF receptors, CRF1 and CRF2 receptors, have been identified and cloned. Centrally administered CRF decreases food intake in both CRF1 receptor null mice and wild-type control mice equally. These results suggest that central CRF2 receptor may mediate the appetite-suppressing effects of CRF and CRF-like peptides.

### Urocortin

Urocortin, an edogenous CRF-related peptide that has a much higher affinity for the CRF2 receptor than CRF, induces more potent anorectic effects than CRF after central administration. A CRF2 receptor-selective antagonist, antisauvagine-30, reverses or attenuates the effects of urocortin and CRF on food intake and body weight.

### Melanin-Concentrating Hormone and Orexins

Orexins (hypocretins) and melanin-concentrating hormone (MCH), neuropeptides localized to the LHA, have an orexigenic effect after central injection. Expression of both MCH and orexin mRNA is increased in response to fasting. MCH-deficient mice reduce food intake and body weight with an increase in metabolic rate. Orexin knockout mice are also hypophagic but have normal body weight, indicating a difference in metabolic rate. These results suggest that these neuropeptides also play a role in the regulation of energy homeostasis.

## SATIETY IN DISEASE

The clinical course of a number of acute and chronic diseases is characterized by the development of a persistent form of satiety, which is called secondary anorexia and is different from anorexia nervosa, a neuropsychiatric disease. Anorexia is usually defined as the loss of the desire to eat and leads to reduced food intake. Unfortunately, anorexia and reduced food intake are often neglected issues in the clinical management of patients, although they have a significant negative impact on morbidity and mortality.

The neurochemical mechanisms responsible for secondary anorexia are still a matter of debate. However, a general consensus exists on at least two issues related to its pathogenesis: (1) multifactoriality and (2) a relationship to disturbances of the previously reviewed central mechanisms controlling food intake under normal conditions. Thus, secondary anorexia might result from defective signals arising from the periphery, errors in the transduction process, or disturbances in the activity of the second-order neuronal signaling pathways. Consistent data suggest that secondary anorexia might be triggered by cytokines, particularly by interleukin-1

(IL-1), IL-6, tumor necrosis factor α, and interferon-γ, which are peptides involved in the modulation of the immune response, exerting biochemical and behavioral effects. They are primarily produced by immune system cells and their mRNA is overexpressed in the hypothalamus of tumor-bearing or septic animals with anorexia.

The mechanisms by which cytokines potentiate satiety during illness are currently under investigation. However, it is likely that cytokines may play a pivotal role in long-term inhibition of feeding by mimicking the hypothalamic effect of excessive negative feedback signaling. This could be achieved by inhibition of the NPY/AgRP orexigenic network, as well as by persistent stimulation of the POMC anorexigenic pathway but also of other networks, including hypothalamic neurotransmission. In this light, the link between cytokines and brain monoaminergic neurotransmission is strengthened by a number of lines of evidence indicating that cytokines, and particularly IL-1, stimulate the release of hypothalamic 5-HT and DA, which directly stimulate melanocortins to induce anorexia. Both monoamines modulate neuronal activity via their action on calcium channels. Neurotransmitters in turn can also affect IL-1-mediated activities. More recently, it has been shown that cytokines potentiate satiety by up-regulating the enzyme cyclooxygenase 2 in the brain, thus resulting in an overexpression of prostaglandin E2 (PGE2). PGE2 may in turn act as a neuromodulator by influencing hypothalamic monoaminergic neurotransmission.

It is also reasonable to speculate that during illness the hypothalamus might influence skeletal muscle wasting, thus synergistically acting with the well-established peripheral cachectic factors. As previously noted, the hypothalamus controls not only energy intake, but also energy expenditure. In pure neurogenic muscular involvement, muscle wasting is secondary to the activation of the same intracellular proteolytic pathways responsible for tumor-induced wasting. In elderly cancer patients, changes in hypothalamic-driven sympatho-vagal balance associated with weight loss have been detected. It is therefore tempting to speculate that, during illness, deranged hypothalamic activity may not only corroborate anorexigenic pathways, but also send proteolytic signals to skeletal muscles.

## See Also the Following Articles

Appetite • Brain–Gut Axis • Cholecystokinin (CCK) • Pancreatic Polypeptide Family

## Further Reading

Batterham, R. L., Cowley, M. A., Small, C. J., Herzhog, H., Cohen, M. A., Dakin, C. L., Wren, A. M., Brynes, A. E., Low, M. J., Ghatei, M. A., Cone, R. D., and Bloom, S. R. (2002). Gut hormone PYY3–36 physiologically inhibits food intake. *Nature* **418**, 650–654.

Broberg, C., and Hokfelt, T. (2001). Hypothalamic and vagal neuropeptide circuitries regulating food intake. *Physiol. Behav.* **74**, 669–682.

Halford, J. C., and Blundell, J. E. (2000). Pharmacology of appetite suppression. *Prog. Drug Res.* **54**, 25–58.

Inui, A. (2001). Ghrelin: An orexigenic and somatotrophic signal from the stomach. *Nat. Rev. Neurosci.* **2**, 551–560.

Kahler, A., Zimmermann, M., and Langhans, W. (1999). Suppression of hepatic fatty acid oxidation and food intake in men. *Nutrition* **15**, 819–828.

Makarenko, I. G., Meguid, M. M., and Ugrumov, M. V. (2002). Distribution of serotonin 5-hydroxytryptamine 1B [5-HT(1B)] receptors in the normal rat hypothalamus. *Neurosci. Lett.* **328**, 155–159.

McMinn, J. E., Baskin, D. G., and Schwartz, M. W. (2000). Neuroendocrine mechanisms regulating food intake. *Obes. Rev.* **1**, 37–46.

Meguid, M. M., Yang, Z.-J., Bellinger, L. L., Gleason, J. R., Koseki, M., Laviano, A., and Oler, A. (1996). Innervated liver plays an inhibitory role in regulation of food intake. *Surgery* **119**, 202–207.

Meguid, M. M., Yang, Z.-J., and Gleason, J. R. (1996). The gut–brain brain–gut axis in anorexia: Toward an understanding of food intake regulation. *Nutrition*, **12**, S57–S62.

Moran, T. H. (2000). Cholecystokinin and satiety: Current perspectives. *Nutrition* **16**, 858–865.

Nandi, J., Meguid, M. M., Inui, A., Xu, Y., Makarenko, I. G., Tada, T., and Chen, C. (2002). Central mechanisms involved with catabolism. *Curr. Opin. Clin. Nutr. Metab. Care* **5**, 407–418.

Plata-Salaman, C. R. (1996). Anorexia during acute and chronic disease. *Nutrition* **12**, 69–78.

Schwartz, G. J., and Moran, T. H. (1996). Sub-diaphragmatic vagal afferent integration of meal related gastrointestinal signals. *Neurosci. Biobehav. Rev.* **20**, 47–56.

Schwartz, M. W., Woods, S. C., Porte, D. Jr., Seeley, R. J., and Baskin, D. G. (2000). Central nervous system control of food intake. *Nature* **404**, 661–671.

Vergani, A. V., and Bertolini, A. (2000). Role of melanocortins in the central control of feeding. *Eur. J. Pharmacol.* **405**, 25–32.

# Secretin

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**desensitization** A rapid process that results in the attenuation of G-protein-coupled receptor responsiveness, despite continuing agonist stimulation.

**G-protein-coupled receptor (GPCR)** An integral membrane-bound protein that consists of a seven-transmembrane α-helical domain. GPCRs are responsible for converting an extracellular signal to an intracellular message via ligand binding and activation of heterotrimeric G-proteins.

**G-proteins** Heterotrimeric guanine nucleotide-binding proteins consisting of three subunits: α, β, and γ. G-proteins are regulatory molecules that mediate intracellular signaling pathways.

**hormone** A Greek word meaning "to excite"; it is used to describe a chemical messenger that induces a specific response in target cells distant from the site of synthesis.

**receptor** A molecular structure within or on the surface of a cell that binds to a specific ligand and initiates a cellular response. The largest class of receptors is the G-protein-coupled receptor family.

**second messenger** An intracellular mediator produced in response to the binding of agonist to its specific receptor. These signaling molecules activate effector molecules either directly or via activation of protein kinases. Examples of second messengers include cyclic AMP, $Ca^{2+}$, and diacylglycerol.

**signaling** A sequential process that results in conversion of an extracellular event into an intracellular message.

**In 1902, Bayliss and Starling observed that a chemical substance in upper intestinal extracts, when injected into anesthetized dogs with denervated intestine, stimulated pancreatic secretion. The discovery of this first hormone, named secretin, was the beginning of the search for many other chemical messengers that, when released from one tissue, travel through the bloodstream and exert their effects on distant tissues in the body. Hence, the name hormone, a Greek word meaning arise to activity, was used to describe these chemical substances.**

## PEPTIDE

Secretin is a basic 27-amino-acid neuroendocrine polypeptide, with a molecular weight of 3055 Da (Table I). The gene encoding human prosecretin is mapped to chromosome 11p15.5. Secretin belongs to a family of peptide hormones with similar amino acid sequences, indicating a common ancestral gene (Table II). The human secretin locus has four exons, which encode a signal sequence, an N-terminal peptide, secretin, and an amidated C-terminal extension peptide. The secretin genes from human, rat, porcine, guinea pig, and canine have been sequenced and demonstrate a high degree of evolutionary conservation.

## TISSUE DISTRIBUTION

Secretin is produced and secreted mainly from specialized cells, known as S cells, in the villi of the small intestine. The secretin-producing cells are found along the entire small intestine. Northern blot analysis has detected human secretin mRNA in the testis, small intestine, and spleen, as well as in different areas of the brain, with the highest level in the medulla.

## RECEPTOR BIOLOGY

Secretin exerts its effects on its target organs via specific cell surface receptors. The secretin receptor belongs to a unique subfamily of receptors known as

TABLE I Amino Acid Sequence of Secretin Peptides

| | |
|---|---|
| Human | H S D G T F T S E L S R L R E G A R L Q R L L Q G L V |
| Dog | H S D G T F T S E L S R L R E S A R L Q R L L Q G L V |
| Rat | H S D G T F T S E L S R L Q D S A R L Q R L L Q G L V |
| Cow | H S D G T F T S E L S R L R D S A R L Q R L L Q G L V |
| Pig | H S D G T F T S E L S R L R D S A R L Q R L L Q G L V |
| Avian | H S D G L F T S E Y S K M R G N A Q V Q K F I Q N L M |

**TABLE II Secretin Family of Gastrointestinal Peptides**

| |
|---|
| Secretin |
| Glucagon |
| Vasoactive intestinal peptide |
| Glucagon-like peptides 1 and 2 |
| Glucose-dependent insulinotropic polypeptide |
| Pituitary adenylate cyclase-activating polypeptide |
| Peptide histidine–isoleucine |

G-protein-coupled receptors (GPCRs), the largest family of receptors identified to date. The secretin receptor contains seven membrane-spanning α-helices, an extracellular amino-terminus, and an intracellular carboxy-terminus (Fig. 1). This receptor is representative of a receptor family that includes receptors for secretin, glucagon, vasoactive intestinal peptide, and many other gastrointestinal peptide receptors.

The secretin receptor shares a common molecular architecture with other members of this family of GPCRs (Table III). The overall primary structure of the secretin receptor has several interesting features; it consists of a long amino-terminal domain that is important for ligand binding and receptor activation, based on studies carried out with either truncated or chimeric receptors. The N-terminal domain contains sites for possible asparagine-linked glycosylation (positions 72, 100, 106, 128, and 291). There are 10 extracellular cysteine residues, 2 of which are involved in linking the first and second extracellular loops, as well as 7 highly conserved residues. Three exoloops and three cytoplasmic loops plus a hydrophilic C-terminal domain separate the putative seven-transmembrane regions.

Ligand binding to the N-terminal of the secretin receptor results in coupling of heterotrimeric guanine nucleotide-binding proteins (G-proteins) at the C-terminal of the receptor. G-proteins are intermediate regulatory molecules that initiate the intracellular signaling process. They consist of three subunits: α, β, and γ. The binding of secretin to its receptor promotes the exchange of GDP for GTP on the $G_\alpha$ subunit, which allows the separation of $G_\alpha$ from the $G_{\beta\gamma}$ subunit. The G-protein subunits then amplify intracellular signals with subsequent activation of the effector molecules such as adenylyl cyclase, phosphodiesterases, phospholipase $A_2$, phospholipase C, and ion channels (Fig. 2). These in turn produce second messengers, including cyclic AMP (cAMP), inositol 1,4,5-trisphosphate, and diacylglycerol.

Termination of the secretin receptor signal is just as important for balanced and normal cellular function as the initiation of signaling. In order to prevent receptor overstimulation, cells have evolved a feedback

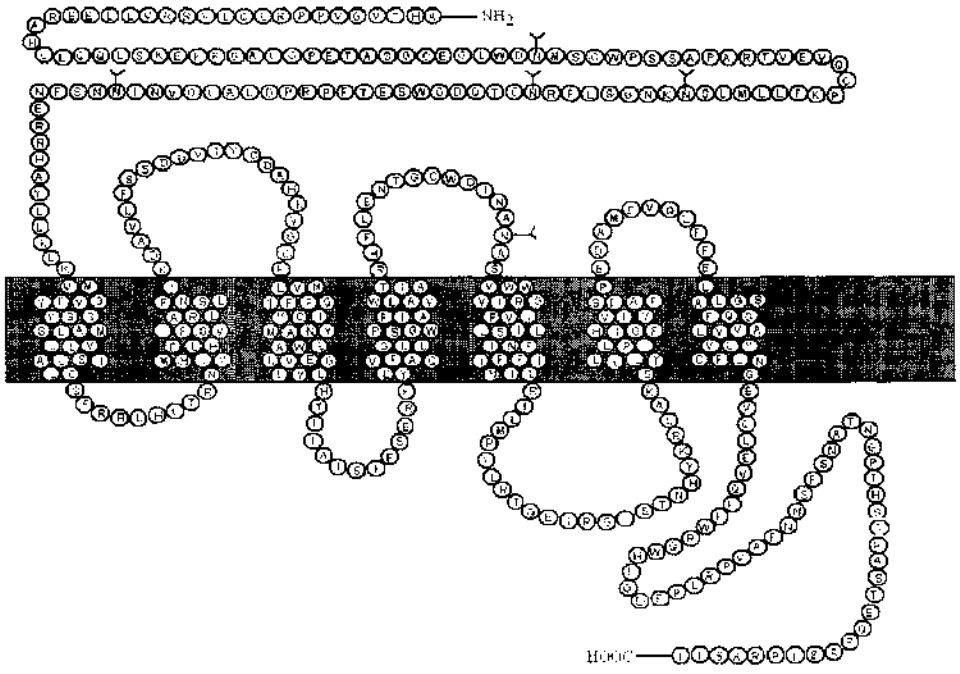

**FIGURE 1** Schematic representation of the general structure of the secretin receptor. This receptor contains a seven-transmembrane α-helical region. The three intracellular loops are important for interaction with G-proteins and contain multiple phosphorylation sites. The N-terminal is important for ligand binding and contains N-linked glycosylation sites.

TABLE III The Secretin Family G-Protein-Coupled Receptors

| |
|---|
| Secretin receptor |
| Parathyroid hormone receptor |
| Glucagon receptor |
| Diuretic hormone receptor |
| PACAP receptor |
| Leukocyte antigen CD97 |
| Vasoactive intestinal peptide receptor |
| Calcitonin receptor |
| Glucagon-like peptide 1 and 2 receptors |
| Corticotropin-releasing factor receptor |
| Growth hormone-releasing factor receptor |
| Cell surface glycoproteins EMR1 and F4/80 |

mechanism called desensitization, by which the receptor becomes less responsive to further stimulation. The signal can be terminated either through receptor down-regulation or by a rapid process that involves two different serine/threonine protein kinases: (1) G-protein-coupled receptor kinases (GRKs) or (2) second messenger-dependent protein kinases. In homologous desensitization, GRK-mediated phosphorylation of the secretin receptor facilitates the binding of cytosolic proteins known as β-arrestins to the receptor followed by receptor endocytosis. In contrast, heterologous desensitization involves second messenger-dependent protein kinases such as protein kinase A (PKA) or protein kinase C, acting on both active and unstimulated receptors. It has been shown that GRK-specific phosphorylation is involved in the rapid attenuation of secretin receptor signaling in HEK 293 cells, whereas secretin receptor internalization occurs via PKA-dependent phosphorylation in the same cell line.

The cDNA for the secretin receptor has been cloned from human, rat, and rabbit. The human secretin receptor consists of 440 amino acids with a molecular weight of approximately 49 kDa. The gene for the secretin receptor is localized on human chromosome 2q14.1.

## FUNCTIONS

Over the years, secretin has been shown to elicit a variety of physiological actions, as well as functional responses at pharmacological serum levels. These functions of secretin are classified as either stimulatory or inhibitory, affecting organs such as the pancreas, liver, and intestine. The essential role of secretin is to regulate pancreatic fluid and bicarbonate secretion, which results in neutralization of acidic chyme from the stomach. Secretin is released from the small intestine in response to

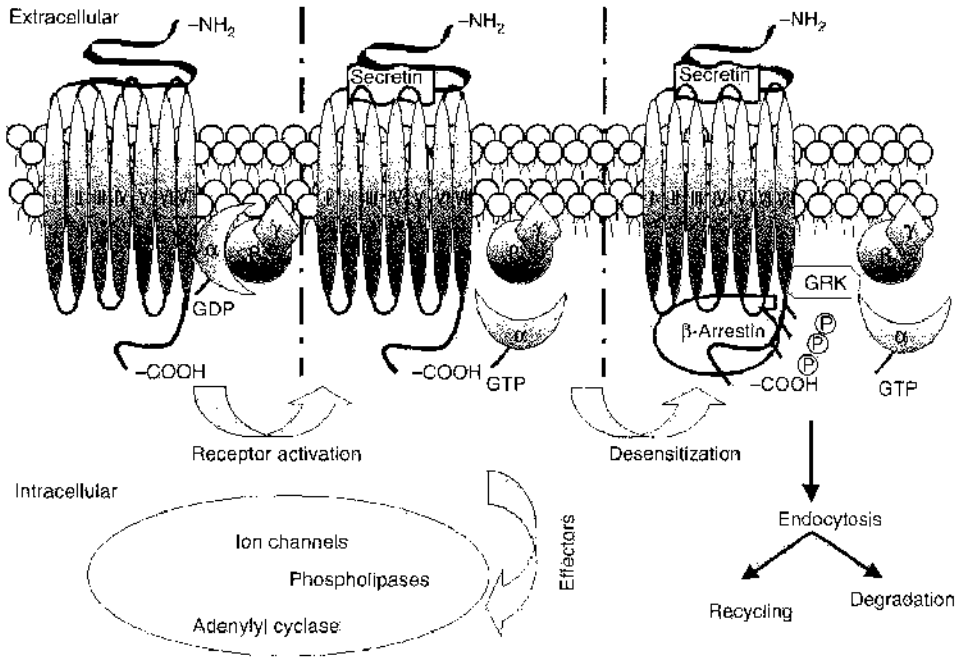


FIGURE 2 Binding of secretin to its receptor results in the exchange of GDP for GTP on the $G_\alpha$ subunit with subsequent dissociation of $G_\alpha$ from the $G_{\beta\gamma}$ subunit, which activates G-protein effectors. β-Arrestin binds to GRK-phosphorylated receptor and uncouples the receptor from its G-protein, initiating receptor endocytosis, which is an important step in receptor dephosphorylation and recycling.

gastric acid and as duodenal pH rises, further release of secretin is curtailed via a negative feedback mechanism. It has been reported that acid-stimulated secretin release is mediated by an endogenous secretin-releasing peptide that is sensitive to trypsin. This peptide stimulates secretin release until sufficient pancreatic proteases degrade secretin-releasing peptide and terminate secretin release. In addition, ingested fats stimulate secretin as they are converted to fatty acids in the gastrointestinal tract.

It has been shown that pharmacological concentrations of secretin have the ability to stimulate gastric pepsin secretion and inhibit gastric acid release, gastrin secretion, and motility of the small intestine. Pharmacological doses of secretin have been shown to increase secretion of a bicarbonate-rich fluid via the biliary tract, increase the lower esophageal sphincter pressure, increase cardiac output, increase renal excretion, increase insulin release, and increase epidermal growth factor production from Brunner's glands in the duodenum. Secretin may also be involved in an early stage in the development of enteroendocrine cells.

Apart from its action on the pancreas, secretin has been found in the central nervous system and may play a role in neurotransmission. For example, secretin increases cAMP levels in different areas of the brain. It has also been suggested that secretin may act as a neurotransmitter through activation of tyrosine hydrolase, an enzyme that is required for the synthesis of catecholamines.

## CLINICAL SIGNIFICANCE

Secretin has been used as a diagnostic tool to evaluate digestive and pancreatic function. The most common clinical use of secretin has been in the diagnosis of patients with Zollinger-Ellison syndrome (gastrinoma). In patients with gastrinoma, administration of secretin causes an increase in gastrin release. Elevated serum gastrin levels are the basis for determining the presence of gastrin-producing tumors. In fasting patients, baseline blood samples are taken 5 min prior to and immediately prior to administration of secretin. Secretin [2 units/kg intravenously (iv)] is given over a 30 s interval and serum samples are taken 2 and 5 min after injection and then at 5 min intervals for 20 min. Baseline serum gastrin levels in patients with gastrinoma are usually greater than 150 pg/ml. The iv secretin stimulation test produces a quick and substantial increase in serum gastrin (>200 pg/ml). A positive response (>200 pg/ml) occurs in over 95% of patients with proven gastrinoma. However, achlorhydria or profound hypochlorhydria can result in increased fasting serum gastrin levels and exaggerate the response to iv secretin stimulation. Patients on acid-suppressive therapy should be studied when they are off these medications. Since secretin is a peptide hormone that increases the volume and bicarbonate content of pancreatic juice, patients with acute pancreatitis should not have this test performed.

Secretin is also used to diagnose pancreatic insufficiency and is given during endoscopic retrograde cholangiopancreatography to assist in ductal cannulation.

The behavior of children with autism has been studied following administration of secretin. Initial observations indicating that secretin improved behavior and social interaction were not supported in a double-blind, placebo-controlled study. Therefore, at present, there is no evidence to support a role for secretin in the treatment of autistic children's behavior. There are no known diseases of secretin.

## SUMMARY

Secretin was the first hormone to be discovered. It is produced primarily by endocrine cells of the small intestine and its primary action is to regulate pancreatic fluid and electrolyte secretion. Secretin exerts its biological effects through specific cell surface receptors. Binding of secretin to its receptor amplifies signals inside the cell, thus activating effector molecules and increasing cAMP levels. Secretin is used clinically in the diagnosis of gastrinomas and pancreatic insufficiency.

### Acknowledgments

This work is supported in part by National Institutes of Health Grants DK02544-04 and DK58828-01 and by the Mal Tyor Scholarship Award in Gastroenterology (to M.A.S).

### See Also the Following Articles

Gastric Acid Secretion • Gastrin • Gastrinoma • Pancreatic Bicarbonate Secretion • Pancreatic Function Tests

### Further Reading

Bayliss, W. M., and Starling, E. H. (1902). The mechanism of pancreatic secretion. *J. Physiol.* 28, 325–353.

Holtman, M. H., Ganguli, S., Hadac, E. M., Dolu, V., and Miller, L. J. (1996). Multiple extracellular loop domains contribute critical determinants for agonist binding and activation of the secretin receptor. *J. Biol. Chem.* 271, 14944–14949.

Ip, N. Y., and Zigmond, R. E. (2000). Synergistic effects of muscarinic agonists and secretin or vasoactive intestinal peptide on the regulation of tyrosine hydrolase activity in sympathetic neurons. *J. Neurobiol.* 42, 14–21.

Leiter, A. B., Chey, W. Y., and Kopin, A. S. (1994). "Secretin" (J. H. Walshand and G. J. Dockray, eds.), pp. 147–173. Raven Press, New York.

Li, P., Lee, K. Y., Chang, T. M., and Chey, W. Y. (1990). Mechanism of acid-induced release of secretin in rats: Presence of a secretin-releasing peptide. *J. Clin. Invest.* 86, 1474–1479.

Rindi, G., Ratineau, C., Ronco, A., Candusso, M. A., Tsai, M.-J., and Leiter, A. B. (1999). Targeted ablation of secretin-producing cells in transgenic mice reveals a common differentiation pathway with multiple enteroendocrine cell lineages in the small intestine. *Development* 126, 4149–4156.

Sandler, A. D., Sutton, K. A., DeWeese, J., Girardi, M. A., Sheppard, V., and Bodfish, J. W. (1999). Lack of benefit of a single dose of synthetic human secretin in the treatment of autism and pervasive development disorder. *N. Engl. J. Med.* 341, 1801–1804.

Shetzline, M. A., Premont, R. T., Walker, J. K., Vigna, S. R., and Caron, M. G. (1998). A role for receptor kinases in the regulation of class II G protein-coupled receptors: Phosphorylation and desensitization of the secretin receptor. *J. Biol. Chem.* 273, 6756–6762.

Walker, J. K., Premony, R. T., Barak, L. S., Caron, M. G., and Shetzline, M. A. (1999). Properties of secretin receptor internalization differ from those of the β2-adrenergic receptor. *J. Biol. Chem.* 274, 31515–31523.

Whitmore, T. E., Holloway, J. L., Lofton-Day, C. E., Maurer, M. F., Chen, L., Quinton, T. J., Vincent, J. B., Scherer, S. W., and Lok, S. (2000). *Cytogenet. Cell. Genet.* 90, 47–52.

# Sensory Innervation

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**afferent fiber** Nerve fibers conducting sensory information from the periphery to the central nervous system. In this context, "sensory" does not necessarily imply sensation.

**dorsal root ganglia** Cell bodies of spinal afferent neurones are located in sensory ganglia on the dorsal root of each spinal nerve. They project centrally to make synaptic connections in the spinal cord and peripherally to terminate in the viscera.

**enteric sensory neurones** Located entirely within the wall of the gastrointestinal tract, the enteric sensory neurones have cell bodies in either the submucosal or myenteric plexus and do not project beyond the gut wall; also referred to as intrinsic primary afferent neurones.

**nociceptor** Sensory nerve endings that are stimulated by tissue injury and can give rise to pain.

**nodose ganglia** Sensory ganglia containing the cell bodies of afferent neurones that innervate the thoracic and abdominal viscera. These neurones project centrally to make synaptic connections in the nucleus of the tractus solitarius and peripherally to terminate in the viscera.

**Sensory neurones are the information superhighway from the gastrointestinal tract to the central nervous system. These neurones have terminations in the gut wall that are specialized to detect changes in the gut environment, and through the generation of trains of action potentials convey the coded information that keeps the central nervous system abreast of events in the bowel. Most of this information goes unperceived but is used to trigger reflexes that coordinate digestive activity according to the needs of the individual. Sensory information also contributes to behavioral mechanisms, particularly those involved in food assimilation, and are integral to satiety and anorexia. Sensory afferents also mediate sensations such as fullness, bloating, nausea, and discomfort. These sensations from the gastrointestinal tract, like visceral pain, generally tend to be vague and poorly localized, often being referred to somatic sites (dermatomes) because of the way visceral and somatic sensory inputs converge in the spinal cord. However, some individuals have heightened visceral sensitivity and this is a hallmark of functional bowel disorders such as irritable bowel syndrome. These patients either generate aberrant sensory signals from the gastrointestinal tract or the normal signals associated with digestion are interpreted inappropriately (or there is a combination of both). Either way, the sensory innervation of the gastrointestinal tract has become a focus for considerable clinical and therapeutic interest.**

## INTRODUCTION

The gastrointestinal tract has to perform manifestly diverse functions. It is responsible for the digestion and absorption of nutrients that are vital to an organism's

survival. Yet, the functional adaptations that favor absorption are also a defense liability. Central to these ostensibly conflicting tasks is the ability to monitor the contents of the gastrointestinal lumen and various aspects of the gastrointestinal function in order to orchestrate appropriate patterns of motility, secretion, and blood flow that, on the one hand, facilitate nutrient absorption and, on the other, rapidly dilute and expel potentially harmful antigenic or pathogenic material through diarrhea and vomiting. The gastrointestinal sensory innervation plays a pivotal role in these processes.

## SCALE OF THE SENSORY INNERVATION

The gastrointestinal tract has an extensive sensory innervation. These sensory neurones terminate at various levels within the gut wall, including muscle, mucosal epithelia, and enteric ganglia. Other endings terminate in the serosa and mesenteric attachments and form a dense network around mesenteric blood vessels and their tributaries in the gut wall. These various endings maintain a steady flow of afferent traffic to the central nervous system (CNS), relating information on activity both within and outside the gut wall. The sensory information is conveyed to the CNS by separate vagal and spinal pathways to the brain stem and spinal cord, where information is processed and projected to higher brain areas. Because these afferent nerves run in bundles that contain the autonomic outflow from the CNS, they are often referred to as parasympathetic and sympathetic afferents, but this is something of a misnomer; these terms refer to motor function. More correctly, the vagal, pelvic, and splanchnic nerves are the routes these afferents follow to the brain stem and spinal cord. Vagal afferents are more prevalent in the proximal gut, and spinal, particularly pelvic, afferents predominate in the distal gut.

Approximately 50,000 vagal afferents are estimated to supply the gastrointestinal tract, outnumbering vagal parasympathetic efferent fibers by about 10:1. There may be a similar number of spinal afferents, with about 7% of sensory cell bodies in the dorsal root ganglia (DRG) projecting to the viscera and a proportion of these innervating the gastrointestinal (GI) tract. The nodose and DRG neurones have axons that project into the CNS, where they synapse with second-order neurones in the brain stem and spinal cord, respectively.

Vagal and spinal afferent fibers are generally unmyelinated or thinly myelinated fibers transmitting different aspects of sensory information at low conduction velocity (~1 m/sec). Vagal neurones generally process physiological information (for example, the nature and composition of the luminal contents and the presence and amplitude of ongoing motor activity of the gut). In contrast, spinal neurones also process pathophysiological information (for example, potentially noxious mechanical or chemical stimuli arising through tissue injury, ischemia, and inflammation). However, vagal and spinal pathways are not entirely functionally separate, because there is some overlap in their sensitivity, particularly between vagal and pelvic afferents, and there is also some interplay between these two pathways.

The enteric nervous system also contains the cell bodies of sensory neurones that play an integral role in the organization of local reflexes. Of the many millions of myenteric neurones, an estimated 30% are sensory, on the basis of their morphology, chemical phenotype, and electrophysiology. Thus the density of the extrinsic nerve terminals in the bowel wall is sparse compared to the terminals of enteric sensory neurones. However, because these intrinsic afferents do not project beyond the bowel wall, they do not contribute to visceral sensations except indirectly as a consequence of reflex changes in secretion, blood flow, or motor activity. Other myenteric neurones project out from the bowel wall and are therefore referred to as intestinofugal fibers. These project to the prevertebral ganglia and make synaptic contact with postganglionic sympathetic neurones that project back to the intestinal wall, again without being directly involved in visceral perception.

## SENSORY ENDINGS

The majority of gastrointestinal afferents terminate within the gut wall as bare nerve endings. Thus, the differential sensitivity of afferents arises from their location in the gut wall, their relationship with other structures, and the receptors and ion channels that they express.

### Vagal Afferents

Vagal neurones terminate predominantly in the mucosa and the muscle. Afferent endings in the mucosa are in close association with the lamina propria adjunct to the mucosal epithelium, but are never exposed directly to the contents of the lumen. Thus, vagal afferents within the mucosa are in a position to monitor the chemical nature of luminal contents either directly following absorption across the mucosal epithelium or

indirectly via other cells in the epithelium that are exposed to luminal content. Mucosal afferents are also exquisitely sensitive to any local mechanical stimulation that deforms the mucosal epithelium.

Vagal afferent endings in the muscle can be classified into two types: intramuscular arrays (IMAs) and intraganglionic laminar endings (IGLEs). IMAs are distributed within the muscle sheets, especially in the longitudinal muscle, parallel to the long axes of muscle fibers. They appear to make direct contact with the muscle fibers, but they also course on, and form appositions with intramuscular interstitial cells of Cajal, which may play a role in mechanotransduction. IGLEs are basketlike structures surrounding myenteric ganglia. Because IGLEs are located between the circular and longitudinal muscle layers, they are exposed to shearing forces generated during muscle stretch or contraction and have been suggested to be a source of mechanosensitivity. Evidence supporting this view has been elaborated recently by mapping the receptor fields of vagal afferent endings in the esophagus and showing morphologically that these "hot spots" correspond to the locations of IGLEs. IGLEs are the primary candidates for conveying mechanosensory information relevant to distension and contraction of the bowel wall. However, another intriguing possibility arising from the close proximity of IGLEs to the myenteric ganglion is that IGLEs are chemosensitive, responding to neurotransmitters and neuromodulators released into the synaptic neuropil. In the absence of clearly defined synapses between IGLEs and myenteric neurons, communication may arise following simple diffusion from the site of release to the afferent nerve terminals. Many cell types (neurons, glial cells, endothelium) and many different kinds of substances (ions, purines, amino acids, monoamines, peptides, gases) released through vesicular or nonvesicular mechanisms could potentially participate in such communication.

### Spinal Afferents

Spinal nerve terminals are distributed throughout the gut wall but are also located in the serosa and mesenteric attachments, often associated with mesenteric blood vessels. Spinal afferents are largely unmyelinated and have multiple branching punctate endings that correspond to multiple receptive fields, often extending over several visceral structures. Their location and response characteristics suggest that spinal afferents respond to distortion of the viscera during distension and contraction. However, spinal afferent terminals are also found in the mucosa. These spinal afferents respond to mechanical stimulation and to the chemical environment within the lamina propria and in particular respond to the changing chemical milieu following injury, ischemia, or infection.

### Axon Reflexes

Spinal afferents have collateral branches that supply blood vessels and innervate the enteric ganglia. These fibers have a beaded appearance and are described as being varicose, with the varicosities being the site of neurotransmitter storage and release. Activation of an afferent terminal causes an action potential to be propagated centrally, but action potentials can also propagate down axon collaterals and stimulate the release of neurotransmitters in a local axon reflex, which serves to modulate blood flow and enteric reflex pathways. The main transmitters present in spinal afferents are calcitonin gene-related peptide (CGRP) and substance P (SP). Both of these peptides are implicated in neurogenic inflammation and so their release via axon reflexes may be involved in the development of an inflammatory response. In addition, CGRP released via local axon reflexes may play a cytoprotective role by increasing blood flow to the mucosa. A small proportion of vagal afferent terminals also contain CGRP and SP, and collateral axon branches have been described, but there is little functional evidence to suggest that axon reflexes occur in vagal neurones.

## ADEQUATE STIMULUS AND SIGNAL TRANSDUCTION

The early literature is filled with anecdotal evidence that gastrointestinal pain is dull, aching, ill-defined, and badly localized. Stimuli such as cutting, crushing, and burning, which cause pain if applied to the skin, are not perceived when applied to patients with open colostomies, for example. One explanation for this is that sensory information from the skin and viscera are processed differently in the CNS. Brain imaging studies in humans have shown that, unlike somatic afferents, which on activation cause the S1 somatosensory cortex to "light up", gastrointestinal stimulation leads to activation of secondary somatosensory areas, including the anterior cingulate and prefrontal cortex. This indicates that visceral information activates divergent pathways in the CNS, ascending in the spinal cord via spinothalamic and spinoreticular pathways and also via the dorsal columns. Within the spinal cord, visceral and somatic inputs can converge onto the same second-order neurone.

This convergence gives rise to the phenomenon of referred pain, whereby pain from visceral organs is felt at a remote area of the body, the classic example being angina pain referred to the left shoulder.

Another important consideration when comparing visceral and somatic afferent sensitivity is that of adequate stimulus. What is adequate for one set of sensory endings in the gut may be inappropriate for another in the skin. A case in point is that of sensitivity to noxious heat. A heat-sensitive ion channel with a threshold of about 42° C is present on a subset of somatic nociceptive neurones. This channel can also be opened by capsaicin, the pungent ingredient of hot peppers, and is therefore referred to as vanilloid receptor ($VR_1$), a member of the transient receptor potential (TRP) family of proteins. $VR_1$ is expressed by most gastrointestinal afferents, but the gut is unlikely to encounter temperature sufficient to activate this channel, suggesting a role other than detecting body temperature. In this respect, protons, at a pH $<6.8$, are also known to activate $VR_1$ and augment thermosensitivity. Low extracellular pH occurs during tissue injury and ischemia, but in the GI tract, most obviously in the stomach, a low pH is the normal luminal environment and proton sensitivity may have particular significance here. However, other ion channels are sensitive to protons—for example, members of the epithelial $Na^+$ channel (ENaC) family such as acid-sensing ion channels (ASICs) and some members of the P2X receptor family that respond to extracellular ATP.

Gut stimuli that readily cause perception include bowel distension and powerful contraction. These then are the adequate stimuli for gastrointestinal mechanosensitive afferents. The locations of sensory endings in the muscle and in the serosal and mesenteric attachments are consistent with this pattern of sensitivity because distension and contraction will generate tension in the muscle layers and concomitant distortion of the serosa and mesenteric attachments. The sensitivity to both stretch and contractions has led to the term "in-series tension receptor," implying that, by analogy with Golgi tendon organs in skeletal muscle, the sensory endings are linked to gut wall connective tissue elements that transmit tension during contraction or when stretched. However, as previously discussed, the IGLEs that lie in parallel with the muscle appear to be the morphological substrate for tension receptors, and thus "in-series" sensitivity may reside in an "in-parallel" location, probably because of the shear forces that are generated within the tissue. The same may be true for serosal and mesenteric afferents, which are clearly not in series with the muscle and in many cases are actually outside the bowel wall. Thus, sensitivity to distension and contraction arises in these endings as a consequence of the distortion of these structures as the bowel wall moves.

Such mechanical deformations are the basis of mechanosensitivity, which is clearly important both for the reflex mechanisms that control gastrointestinal function and for visceral pain processing. Mechanosensitivity can arise indirectly as a consequence of mechanical forces, causing the release of a chemical mediator that in turn acts on a receptor present on the afferent nerve terminal. ATP, potentially one such substance that is released by mechanical distortion, can act on P2X receptors on the nerve terminal. The P2X receptor is an ion channel that, on activation, leads to depolarization and the generation of action potentials. In contrast, direct mechanosensitivity arises because of the presence of mechanically sensitive ion channels in the nerve terminal membrane. Mechanical deformation of the nerve ending leads to the opening or closing of ion channels, allowing charged molecules to pass in or out of the cell, which in turn leads to an alteration in the excitability of the nerve terminal. A variety of mechanosensitive ion channels have been identified, including a class of receptors exemplified by the ENaC/degenerin family. However, at present, the ion channels and receptors that underlie mechanosensitivity in the gastrointestinal tract remain unknown.

## STIMULUS–RESPONSE FUNCTION

The relationship between the intensity of stimulation and the degree of activation of sensory afferent is known as the stimulus–response function. Afferent information conveyed by spinal and vagal mechanosensitive afferents is somewhat different in its sensory–response function, as revealed by direct electrophysiological recordings of afferent traffic en route to the CNS. When the bowel is distended, vagal muscle mechanoreceptors have low thresholds of activation, responding to pressure rises of just a few millimeters of Hg, and reach maximal responses within physiological levels of distension. These are referred to as low-threshold mechanoreceptors and convey information relating to normal physiological events in the bowel. These endings also respond during contraction and therefore signal to the CNS information relevant to each and every contraction that occurs anywhere along the length of the GI tract. Many spinal afferents also have low thresholds for activation but continue to respond beyond the physiological range and thus encode both physiological and noxious levels of stimulation; these are called wide-dynamic-range fibers. These spinal endings can contribute to signaling visceral pain through some intensity code that recognizes

extreme levels of distension or contraction. Other spinal afferents, particularly those with endings in the serosa and mesenteric attachments, respond only to noxious levels of distension (high-threshold mechanoreceptors) and are referred to as nociceptors. These only respond when the bowel is overdistended or during powerful contractions that distort the bowel.

The factors that determine the sensitivity of low, wide-dynamic-range, and high-threshold mechanosensitivity may include the location of the endings within the bowel wall, the latter being influenced by the extent to which mechanical forces are distributed and dissipated by nonneural structures in the bowel wall. Different mechanosensitive channels may also contribute to their different stimulus–response functions. An extreme example of mechanosensitivity has been described in sensory endings that fail to respond even to severe levels of distension. These are the "sleeping," or silent, nociceptors, which can be awakened to become mechanically sensitive under conditions of injury or inflammation (see later). The latter illustrate the fact that mechanosensitivity is not fixed either in terms of threshold for activation or in gain in the stimulus–response relationship, and as such the threshold can be reduced and the gain increased after injury or during inflammation. Under these conditions, the afferents are sensitized and this process is believed to underlying hypersensitivity observed in some clinical conditions.

## CHEMOSENSITIVITY

An enormous range of chemical mediators can influence the sensitivity of visceral afferents. Luminal nutrients, for example, are transferred across the epithelium to reach the afferent nerve terminals that lie in the lamina propria. Other chemicals are released from within the epithelia following detection of certain contents of the intestinal lumen and are important for initiating reflex mechanisms that optimize digestion and absorption or trigger expulsion via vomiting or diarrhea. Yet other chemicals are released from the many and varied cell types that are present in the gut wall and that are part of the process of immune surveillance. Electrophysiological, immunocytochemical, and molecular biological techniques have revealed the functional expression of receptors to various mediators on the cell bodies of visceral sensory neurons in the dorsal root or nodose ganglia or on their processes in the gut wall. These diverse mediators, which include amines, purines, prostanoids, proteases, and cytokines (Fig. 1), produce their effects on visceral afferent nerves by three distinct processes: (1) by direct activation, which ultimately involves the opening of ion channels present on the nerve terminals, (2) by sensitization, which may occur in the absence of a direct stimulation, but which usually results in afferent hyperexcitability to both chemical and mechanical modalities (this may arise following G-protein-coupled alterations in second messenger systems, which often lead to phosphorylation of membrane receptors and ion channels that control excitability), and (3) by altering the phenotype of the afferent nerve—for example, through alterations in the expression of mediators, channels, and receptors or modulating the activity of these by changing the ligand-binding characteristics or coupling efficiency of other receptors. Neurotropins, in particular nerve growth factor (NGF) and glial cell-derived neurotropic factor (GDNF), influence different populations of visceral afferents and play an important role in adaptive responses to nerve injury and inflammation.

### Chemotransduction

Mediators that produce a direct stimulation of visceral sensory nerve endings may do so as part of a discrete sensory signaling pathway. In this case, the afferent neurone does not respond directly to a particular stimulus, but does so following the release of a mediator from another cell that functions as the sensory detector. One example of such primary sensory cells is the gustatory receptors on the tongue. Cells subserving a similar function in the gut, and often referred to as intestinal "taste" cells, include enterochromaffin (EC) cells, which release 5-hydroxytryptamine (5-HT), and enteroendocrine cells, which release many peptides, including cholecystokinin (CCK), peptide YY (PYY), secretin, and melatonin. The apical tuft of microvilli on these cells is exposed to the intestinal lumen and is proposed to monitor luminal contents; in response to an appropriate stimulus, it releases the contents of storage granules across the basolateral membrane to stimulate afferent terminals in close proximity within the lamina propria. Evidence suggests that these different mediators may act on distinct subpopulations of vagal mucosal afferent nerves. As such, this sensitivity represents an example of a high-fidelity, modality-specific signal transduction pathway. This mechanism, more than likely, functions in the detection of moment-to-moment changes in luminal composition and operates, in the main, below the level of consciousness. However, 5-HT derived from the intestinal mucosa, acting on vagal afferent fibers, is implicated in protection from ingested toxins and is a powerful trigger for vomiting and the associated nausea. In contrast, CCK is a satiety hormone that via vagal activation plays a pivotal role in the control of food intake. In

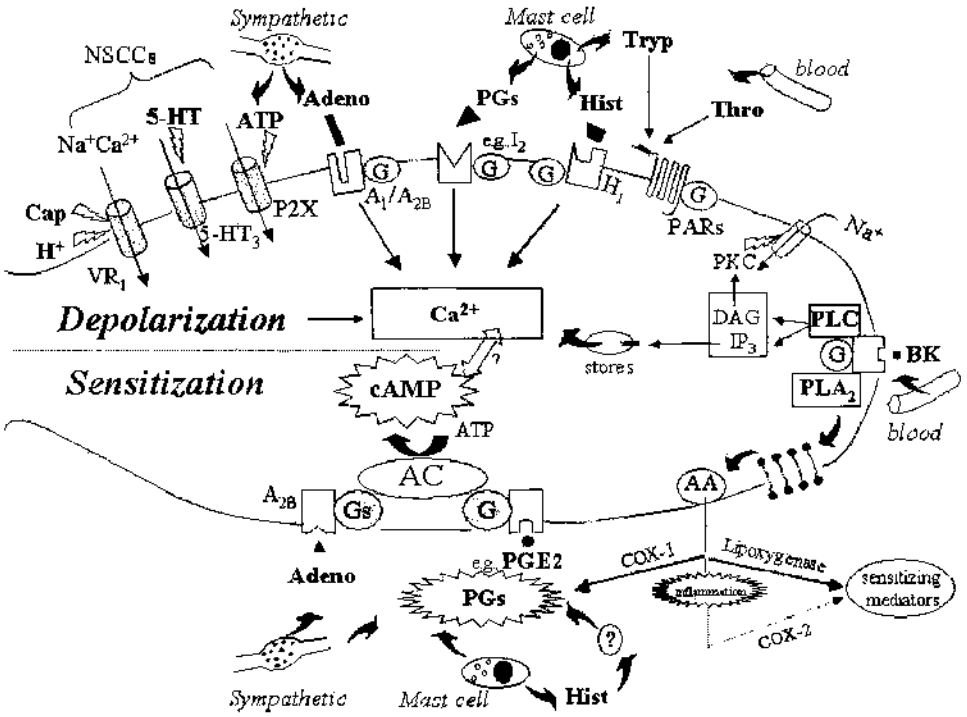


FIGURE 1 Some of the potential receptor mechanisms underlying activation and sensitization of gastrointestinal sensory afferents. Mediators such as serotonin (5-hydroxytryptamine; 5-HT) cause activation, whereas others, such as prostaglandin E2 (PGE2), sensitize visceral afferent responses to other stimuli. Others still, e.g., adenosine (Adeno), cause both stimulation and sensitization, possibly through distinct receptor mechanisms. Bradykinin has a self-sensitizing action, stimulating discharge through activation of phospholipase C (PLC) and enhancing excitability via prostaglandins (PGs) following activation of phospholipase $A_2$ ($PLA_2$). Inflammatory mediators can be released from different cell types (e.g., sympathetic nerves, mast cells, and blood vessels) present in or around the afferent nerve terminal. 5-HT, adenosine triphosphate (ATP), and capsaicin (Cap) can directly activate nonselective cation channels (NSCCs) whereas adenosine, histamine, prostaglandins (not PGE2), and proteases such as mast cell tryptase (Tryp) and thrombin (Thro) act on G-protein-coupled receptors, leading to a $Ca^{2+}$-dependent modulation of ion channel activity. Sensitization, however, may be mediated by elevated levels of intracellular cyclic adenosine 3′,5′-monophosphate (cAMP). Adenosine and PGE2 can generate cAMP directly through G-protein-coupled stimulation of adenylate cyclase (AC). In contrast, histamine may act indirectly through the generation of prostaglandins. The actions of cAMP downstream may involve modulation of ion channels, interaction with other second messengers (e.g., $Ca^{2+}$), or even changes in receptor expression. Other abbreviations: $VR_1$, vanilloid receptor; PARs, protease-activated receptors; PKC, protein kinase C; BK, bradykinin; COX-1, COX-2, cyclooxygenase-1 and -2; AA, arachidonic acid; DAG, diacylglycerol; $IP_3$, inositol 1,4,5-trisphosphate. Modified from Kirkup *et al.* (2001), with permission from the American Physiological Society.

this respect, recent data suggest that other satiety factors, e.g., leptins, orexins, and ghrelin, may interact with CCK signals at the level of the vagal afferent nerve terminal.

Also implicated in sensory signal transduction are the epithelial "brush cells." These differ from EC cells in that they do not have storage granules within the basolateral aspect of the cell. They are morphologically similar to receptor cells within lingual taste buds and express similar G-protein-coupled receptors (for example, α-gustducin), suggesting they play a role in chemosensitivity. However, the way in which brush cells transfer these signals to sensory afferents is currently unknown.

## Promiscuous Chemosensitivity

In contrast to the specific signaling pathways that exist in vagal mucosal afferents, it is apparent that a battery of mediators can influence the sensitivity of

spinal afferents in a more promiscuous manner. Such substances are usually released under conditions of inflammation, injury, or ischemia from a plethora of cell types, e.g., platelets, leukocytes, lymphocytes, macrophages, mast cells, glia, fibroblasts, blood vessel cells, muscle cells, and neurons. Each of these specific cells (e.g., mast cells) may release several of these modulating agents, some of which may act directly on the sensory nerve terminal and some of which may act indirectly, following release of other agents from other cells in a series of cascades.

The net effect of this promiscuous chemosensitivity is that the properties of sensory neurones can change (often referred to as plasticity). Of clinical relevance is the increased sensitivity to both mechanical and chemical stimulation that may contribute to chronic pain states. Moreover, because these afferents also serve to trigger reflex mechanisms that control and coordinate gut function, their sensitization may also cause hyper- or dysreflexia. Sensory neuronal plasticity may have a rapid onset, and this is described as peripheral sensitization because the changes take place at the level of the sensory nerve terminal following release of a great many algesic chemicals. Some of the key mediators, their cellular source, and their action on visceral afferents are illustrated in Fig. 1. Following sensitization, there is a leftward shift in the stimulus–response function, which means that for a given level of stimulation, there is a greater afferent barrage generated. This can give rise to altered perception such that stimuli that are normally innocuous can cause pain and the response to a painful stimulus becomes exaggerated (hyperalgesia). Peripheral sensitization normally develops rapidly and is relatively short-lived. However, in the presence of maintained injury or inflammation, the sensitization can be prolonged, and this depends on changes in gene expression. Genes influenced in this way include those that determine the amount and pattern of neurotransmitters released from the central nerve terminals in the brain and spinal cord, thus altering the way sensory signals are relayed within the CNS. This is the basis of central sensitization. Other genes influence signal transduction and sensory neuronal excitability. Voltage-gated sodium channels are one example of a family of ion channel, some of which play an important role in regulating pain thresholds.

## CONCLUSION

Afferent fibers convey a vast amount of sensory information to the brain stem and spinal cord, but the nature of this information is different for vagal and spinal pathways. Vagal afferents convey predominantly physiological information, whereas spinal afferents are also able to encode noxious events. These spinal nociceptors are influenced by peripherally acting chemicals, released during inflammation and injury, which are thought to trigger the processes leading to sensitization and increased nociceptive activity. Other chemicals act in a more selective way to activate vagal afferents and are implicated in nutrient signaling from the GI tract.

### See Also the Following Articles

**Autonomic Innervation • Brain–Gut Axis • Calcitonin Gene-Related Peptide (CGRP) • Cholecystokinin (CCK) • Enteric Nervous System • Interstitial Cells of Cajal • Parasympathetic Innervation • Substance P • Vagus Nerve**

### Further Reading

Boucher, T. J., and McMahon, S. B. (2001). Neurotrophic factors and neuropathic pain. *Curr. Opin. Pharmacol.* 1(1), 66–72.

Buchan, A. M. (2000). Nutrient tasting and signaling mechanisms in the gut III. Endocrine cell recognition of luminal nutrients. *Am. J. Physiol. Gastrointest. Liver Physiol.* 277, G1103–G1107.

Cervero, F., and Laird, J. M. (1999). Visceral pain. *Lancet* 353, 2145–2148.

Gebhart, G. F. (2000). Pathobiology of visceral pain: Molecular mechanisms and therapeutic implications IV. Visceral afferent contributions the pathobiology of visceral pain. *Am. J. Physiol. Gastrointest. Liver Physiol.* 278, G834–G838.

Holzer, P. (2001). Gastrointestinal afferents as targets of novel drugs for the treatment of functional bowel disorders and visceral pain. *Eur. J. Pharmacol.* 429, 177–193.

Kirkup, A. J., Brunsden, A. M., and Grundy, D. (2001). Receptors and transmission in the brain–gut axis: Potential for novel therapies. I. Receptors on visceral afferents. *Am. J. Physiol. Gastrointest. Liver Physiol.* 280, G787–G794.

Raybould, H. E. (1998). Does your gut taste? Sensory transduction in the gastrointestinal tract. *News Physiol. Sci.* 13, 275–280.

Wood, J. N. (2000). Pathobiology of visceral pain: Molecular mechanisms and therapeutic implications II. Genetic approaches to pain therapy. *Am. J. Physiol. Gastrointest. Liver Physiol.* 278, G507–G512.

Zagorodnyuk, V. P., and Brookes, S. J. (2000). Transduction sites of vagal mechanoreceptors in the guinea pig esophagus. *J. Neurosci.* 20, 6249–6255.

# Serotonin

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**APUDoma** Amine precursor uptake and decarboxylation tumor; another name for neuroendocrine tumor.

**argentaffin cells** Containing a potent reducing agent, usually serotonin, that reduces added silver salts to a black pigment in a manner analogous to development of photographic film.

**argyrophil cells** Neuroendocrine in nature, but do not store serotonin; after exposure to silver salts, an external reducing agent has to be added to reduce the silver salts to a black pigment.

**body mass index** Measure of body fat, derived as (weight in kilograms)/(height meters)$^2$ or (weight in pounds)/(height inches)$^2$ x 703.1. A body mass index of 30.0–34.9 is obese; > 40 is extremely obese.

**carcinoid tumors** Arise from the neuroendocrine cells found throughout the body; the most frequent origin is from the gastrointestinal tract or bronchus. Many, but not all, release neurohormonal agents such as serotonin.

**diarrhea** Increase in frequency, weight, or consistency of stools; patients with stool weights of greater than 200 g/day are usually considered to have diarrhea.

**enterochromaffin cells** Diffuse system of cells in the submucosa of the intestinal tract; contain potent reducing agents, such as serotonin or epinephrine, which can reduce chromium salts that are added during tissue fixation. This forms a brown pigment that is visible in the cells when they are examined with a microscope.

**irritable bowel syndrome** Part of the group of functional gastrointestinal disorders seen frequently by gastroenterologists; patients have chronic and recurrent gastrointestinal symptoms such as abdominal pain, bloating, diarrhea, and constipation. Because there is no known structural basis, the syndrome is thought to be due to altered sensory or motor regulation of the gastrointestinal tract.

**neuroendocrine system** Group of cells with both neural and endocrine characteristics; thought to arise from cells that migrate from the dorsal neural crest area of the embryo during embryological development.

**neuroendocrine tumors** Can arise from the cells of the neuroendocrine system; include carcinoid tumors, pheochromocytomas, pancreatic islet cell tumors, and medullary carcinoma of the thyroid.

**serotonin** Amine (5-hydroxytryptamine) synthesized from the amino acid L-tryptophan; has potent biological effects.

**Serotonin, a neurotransmitter that is synthesized from the amino acid L-tryptophan, exerts its biological effects after it attaches to a variety of serotonin receptors that are present on cell membranes. Serotonin has both physiological and pathological effects. Serotonin is the predominant neurohormone secreted from carcinoid tumors and is responsible for most of the symptoms. Serotonin agonists can increase intestinal motility and serotonin antagonists can ameliorate some forms of irritable bowel syndrome. Selective serotonin reuptake inhibitors are used to treat patients with affective disorders and have been used in the treatment of severe obesity, although they can have negative side effects on the cardiovascular system. Serotonin antagonists markedly decrease the severe nausea and vomiting experienced by patients who receive antineoplastic chemotherapy.**

## INTRODUCTION

The gastrointestinal and circulatory systems have played important roles in the discovery of serotonin. In 1868, it was noted that there was a factor in defibrinated blood that increased vascular resistance in perfused muscle. In 1939, Dr. Vitorio Erspamer in Parma, Italy, discovered enteramine, a substance released from the enterochromaffin system of the gastrointestinal tract that increased intestinal peristalsis. In 1948, Drs. Page, Rappaport, and Green in Cleveland, Ohio, isolated and identified the vasoconstricting substance in defibrinated blood as serotonin. In 1948, Erspamer determined that enteramine was also serotonin. In the ensuing 50 years, studies have indicated that serotonin probably existed in plants even before it existed in animals. There have been numerous studies on the role of serotonin in health and disease. The focus in this article is on the important role of serotonin in medical problems encountered by gastroenterologists.

## SYNTHESIS AND METABOLISM

Serotonin is synthesized from the essential amino acid L-tryptophan. L-Tryptophan is first converted to

 

5-hydroxytryptophan by the enzyme tryptophan hydroxylase. 5-Hyroxytryptophan is then converted to serotonin by the enzyme aromatic amino acid (L-dihydroxyphenylalanine; L-DOPA) decarboxylase. Serotonin(5-hydroxytryptamine; 5-HT) is the biologically vasoactive substance. Because tryptophan hydroxylase is predominantly located in the GI tract and the brain, these areas are the major sites of serotonin production and storage. Some of the 5-HT is secreted into the vascular compartment. Although blood platelets cannot synthesize 5-HT, a major portion of the secreted 5-HT is taken up and stored in the dense granules of platelets. A small but biologically important portion remains free in the plasma.

Three different enzymes inactivate serotonin. Monoamine oxidase oxidatively deaminates serotonin to the intermediate 5-hydroxyindoleacetaldehyde. This aldehyde is then converted to 5-hydroxyindoleacetic acid (5-HIAA) by the enzyme aldehyde dehydrogenase or to 5-hydroxytryptophol by the enzyme alcohol dehydrogenase. In humans, the major pathway is to 5-HIAA. To assess serotonin production, serotonin can be measured in serum, platelets, blood, or plasma. The 24-hour urinary excretion of 5-HIAA or, if the methodology is available, the 24-hour urinary excretion of serotonin can also be measured.

## PHYSIOLOGICAL EFFECTS

Circulating serotonin attaches to serotonin receptors that are located on the cell membrane. There are seven different serotonin receptor classes designated 5-HT1 through 5-HT7. Within each class, subtypes are further designated by an additional letter (e.g., 5-HT1A or 5-HT1B). These serotonin receptors are coupled to a so-called G protein that delivers serotonin-stimulated intracellular messages. However, the exact mechanism of stimulation is not known for all of the serotonin receptor subtypes. The 5-HT4 subtype is positively coupled to adenylyl cyclase. Various medications are agonists (stimulators) of specific serotonin subtypes, and other medications are antagonists (blockers) of specific serotonin subtypes. The serotonin subtypes mediate a variety of physiological responses; in the GI tract, responses include activation of secretory cells, afferent and efferent neuron activation, and direct effects on gut smooth muscle resulting in either smooth muscle contraction or smooth muscle relaxation.

One model that has proved useful in understanding serotonin action is the synaptic cleft. This is the space between a serotonin-secreting neuron and a serotonin-responding neuron that contains the serotonin receptors. The serotonin-secreting neuron not only secretes serotonin, but it also takes up the secreted serotonin that is in the space between the two neurons. The longer the serotonin remains in the synaptic cleft, the greater effect it has on the serotonin-responding neuron. A number of drugs decrease the rate of reuptake of serotonin, thus prolonging the action of the secreted serotonin.

## PHARMACOLOGICAL REGULATION

Many medications can lower the synthesis or release of serotonin through a variety of different mechanisms. Parachlorophenylalanine is a potent inhibitor of tryptophan hydroxylase, the rate-limiting enzyme in the synthesis of serotonin. Administration of this drug dramatically lowers tissue levels of serotonin, and although it is no longer in clinical use, this drug has contributed much to the knowledge of serotonin action. Octreotide acetate, a synthetic analogue of the natural hormone somatostatin, decreases secretion of serotonin from normal tissues and from carcinoid tumors. A large variety of medications are antagonists of various classes and subtypes of serotonin receptors. These medications, including methysergide maleate, cyproheptadine, buspirone, and clozapine, decrease the physiological effect of biologically available serotonin.

Some medications potentiate the effect of biologically available serotonin by blocking its reuptake from the synaptic cleft. They include first-generation antidepressants such as amitriptyline, second-generation antidepressants such as trazodone, and third-generation antidepressants such as fluoxetine. Although first- and second-generation antidepressants also block the reuptake of norepinephrine, third-generation antidepressants block only the reuptake of serotonin. They are thus called selective serotonin reuptake inhibitors (SSRIs). A second mechanism of increasing the effect of serotonin is to use serotonin agonists that bind to specific subtypes of serotonin receptors. Two examples of this class of drugs are the 5-HT4 agonist cisapride, used in treating GI disease, and the 5-HT1D agonist sumatriptan succinate, used in treating migraine and cluster headaches. Finally, monoamine oxidase (MAO) inhibitors such as tranylcypromine and phenelzine inhibit MAO in the liver and other tissues. Because of the reduced inactivation of serotonin, serotonin levels can increase in the body. Clinicians must be careful not to prescribe medications such as an MAO inhibitor and a specific serotonin reuptake inhibitor for simultaneous administration because of the potential for patients to develop dangerously high concentrations of serotonin.

## IRRITABLE BOWEL SYNDROME

The GI tract has played a unique role in the investigation of serotonin and its actions. Because of the enterochromaffin cells in the submucosa of the small intestine, the small intestine has the largest concentration as well as the greatest total quantity of serotonin in the human body. The first evidence that there were distinct types of serotonin receptors came from the work of Gaddum and Picarelli on isolated sections of ileum in 1957. These investigators showed that activation of cholinergic nerves by serotonin and a separate direct action of serotonin on smooth muscle were due, respectively, to an M receptor (now called 5-HT3) and a D receptor (now called 5-HT2).

Cisapride, a 5-HT4 receptor agonist, enhances the release of acetylcholine in the myenteric plexus. Cisapride has been used to stimulate intestinal motility, to increase lower esophageal sphincter pressure for the treatment of nocturnal symptoms of gastroesophageal reflux disease (GERD), and in the treatment of diabetic enteropathy. The greatest success in modifying serotonin action has been in the treatment of a type of irritable bowel syndrome in women in which diarrhea is the predominant symptom. Alosetron (Lotronex) is a highly selective and long-acting 5-HT3 receptor antagonist. This drug is effective in decreasing the troublesome symptoms of this group of patients.

## DEPRESSION

Serotonin has played a major role in our understanding of psychiatric disease. Although dopamine has been the principal neurotransmitter thought to be involved in schizophrenia, there is evidence that serotonin may also be relevant to this problem. A number of effective medications used in treating schizophrenia, such as clozapine, sertindole, and resperidone, are 5-HT2 receptor antagonists. Serotonin may also play a role in anxiety attacks, based on evidence that buspirone, a 5-HT1A and 5-HT2 antagonist, is effective in treating patients with this problem.

Serotonin plays a major role in the treatment of affective disorders such as depression and mania. It is thought that decreased serotonin activity in certain areas of the brain is associated with depression. The administration of first-, second-, and third-generation antidepressants increases serotonin action. Third-generation antidepressants such as fluoxetine, which have a specific action on serotonin and little effect on norepinephrine, have markedly improved the ability of all clinicians to treat patients with depression effectively.

## APPETITE AND OBESITY

Obesity, which is defined as a body mass index of over 30, has become a major problem in the United States. Of even greater concern are extremely obese patients, who are defined as having a body mass index of over 40. This degree of obesity exacerbates diabetes mellitus, coronary artery disease, and hypertension. The ventromedial hypothalamus plays an important role in the regulation of food intake. It contains both an appetite center and a satiety center. This area of the brain has a high concentration of serotonin and norepinephrine. There is evidence that 5-HT2C receptors in this region play a key role in appetite regulation.

Although behavior modification of exercise and diet are the cornerstones of the treatment of obesity, attempts have been made to reduce food intake with medications such as amphetamine and dextroamphetamine. Unfortunately these medications are not suitable for clinical use because they cause a generalized stimulation of the brain, they soon lose their effect on decreasing appetite, and they can be habit forming. Other medications that have been used to decrease appetite include fenfluramine and dexfenfluramine. These medications both inhibit the reuptake of serotonin and cause an increase in the secretion of serotonin from the brain. Many patients have received both fenfluramine and phentermine, a combination that is popularly known as Fen-Phen. Although these medications have helped many obese patients to lose weight, a significant number of patients receiving them developed pulmonary hypertension and others were reported to develop fibrosis of the mitral and aortic valves. Because of this, fenfluramine and dexfenfluramine have been withdrawn from the market. There remains controversy about the long-term significance of the valvular problem.

Sibutramine is the only medication that alters serotonin action that is presently on the market in the United States. Like fenfluramine, sibutramine is a serotonin reuptake inhibitor. However, in contrast to fenfluramine, sibutramine does not stimulate release of serotonin from the brain. Because of reports linking sibutramine administration to increases in blood pressure and heart rate, the Italian Health Ministry has just suspended sales of this drug in Italy. The Food and Drug Administration continues to approve its use in the United States.

## NAUSEA AND VOMITING

Nausea is the subjective sensation of an impending urge to vomit. Vomiting is the forceful ejection of gastroesophageal contents from the mouth. Nausea and

vomiting are nonspecific responses to a variety of agents. However, the nausea and vomiting that has been most resistant to therapy is provoked by cancer chemotherapy agents such as cisplatinum, doxirubicin, and cyclophosphamide. Although many antiemetic agents have been used to treat chemotherapy-induced nausea and vomiting in the past, the first truly effective agent was metoclopramide. Because metoclopramide is a dopamine receptor antagonist, its antiemetic activity was originally attributed to this mechanism. It subsequently became clear that in the high doses in which it is administered, metoclopramide also blocks 5-HT3 receptors.

When the potent and specific 5-HT3 receptor antagonist ondansetron was developed, it was evaluated in many cancer chemotherapy centers. Ondansetron is extremely effective in blocking chemotherapy-induced nausea and vomiting. It is as effective after oral administration as it is after parenteral administration. Although there are 5-HT3 receptors in the brain and in the small intestine, it is thought that ondansetron works by blocking the 5-HT3 receptors in the intestine. Two additional 5-HT3 antagonists, granisetron and dolasetron, are also now available. All three 5-HT3 antagonists are equivalent in their clinical efficacy in cancer chemotherapy patients and are very valuable in allowing patients to avoid the severe nausea and vomiting that accompany treatment. However, the three antiemetic agents do not completely prevent the delayed nausea and vomiting that may occur 24 hours after chemotherapy. Metoclopramide and high-dose dexamethasone may be helpful in ameliorating this delayed response. Because all of these antiemetics are expensive, there has not yet been much clinical experience in evaluating these agents for nausea and vomiting of other etiologies.

## CARCINOID TUMORS AND CARCINOID SYNDROME

### Clinical Manifestations

The term *Karzinoide* (carcinoid) was used by S. Oberdorfer in Germany in 1907 to describe small-intestinal tumors that histologically resembled, but did not behave in the aggressive manner of, adenocarcinomas. In 1952, some patients harboring carcinoid tumors were reported to develop carcinoid syndrome, consisting of diarrhea, facial flushing, and heart valve lesions. In 1953, the chemical released from the carcinoid tumor was identified as serotonin.

Carcinoid tumors are the most common neuroendocrine tumors in clinical practice. Data from evaluation of 840 patients with carcinoid tumors over a 30-year period in one clinical practice are detailed in Table 1, showing the site of tumor origin. Two-thirds of the tumors originated from the ileum, the bronchus, or an unknown site; the remaining one-third of the tumors arose from 17 other diverse sites.

Patients with carcinoid tumors of small-intestinal origin have presenting problems of chronic abdominal pain, bowel obstruction, diarrhea, and facial flushing. During the course of their illness, many develop fibrosis of the pulmonic and tricuspid heart valves, leading to carcinoid heart disease. Some patients require cardiac surgery with replacement of the damaged heart valves.

Although patients with carcinoid tumors can live for a long time, ultimately the illness results in the death of many of the patients. The survival time of patients, from the date of diagnosis to date of death, ranges from 1 day to 260 months, with a mean survival time of 36 months. At the time of death, 10% of the patients were younger than 40 years old and 50% of the patients were younger than 60 years old, an indication of the deleterious effect of carcinoid tumors.

The stage of the disease at the time of diagnosis is the most important factor in determining prognosis. In descending order of survival are patients with localized disease, regional metastasis, and distant metastases. Site of origin also plays a role in prognosis, in that patients with ileal carcinoid tumors and distant metastases have a better prognosis than do patients with pancreatic carcinoid tumors and distant metastases.

The major features of carcinoid syndrome are diarrhea, facial flushing, and heart valve disease. In

**TABLE 1 Origin of Carcinoid Tumors of 840 Patients[a]**

| Origin | Number of patients | Percent of total |
|---|---|---|
| Ileum | 226 | 26.9 |
| Unknown | 198 | 23.6 |
| Bronchus | 162 | 19.3 |
| Pancreas | 58 | 6.9 |
| Stomach | 40 | 4.8 |
| Appendix | 34 | 4.0 |
| Rectum | 34 | 4.0 |
| Duodenum | 21 | 2.5 |
| Cecum | 20 | 2.4 |
| Jejunum | 15 | 1.8 |
| Thymus | 15 | 1.8 |
| Ampulla of vater | 8 | 1.0 |
| Miscellaneous | 5 | 0.6 |
| Meckel's diverticulum | 4 | 0.5 |

[a] Patients evaluated by the author over a 30-year period in the author's clinical practice.

previously published reports, it has been estimated that only 6% of patients with carcinoid tumors had carcinoid syndrome and it was assumed that only these patients had serotonin overproduction. A policy of measuring serotonin production in all patients with carcinoid tumors regardless of the presence or absence of symptoms, however, leads to quite different conclusions: there is evidence of serotonin overproduction in 53% of the patients with carcinoid tumors (personal experience). Even this represents a minimal estimate, because the presence of carcinoid tumors—particularly tumors originating in the bronchus—is not always suspected before surgery. Thus, by the time serotonin production can be evaluated in some patients, the tumor has already been resected. Indeed, measurement of serotonin production in 44 consecutive patients with definite carcinoid tumors still present in their body has provided evidence of serotonin overproduction in 84% of the patients (personal experience).

Although carcinoid tumors can secrete a variety of neurohormones, serotonin is almost certainly responsible for the symptomatic diarrhea. Serotonin, along with other neurohormones, also plays a role in the facial flushing. When patients with carcinoid tumors and increased serotonin production are questioned about symptoms of facial flushing and diarrhea, alone or in combination, the results are surprising: 44% report both diarrhea and facial flushing, 17% report diarrhea but no facial flushing, 6% report facial flushing but no diarrhea, and 33% report neither diarrhea nor facial flushing. The total absence of classical symptoms of carcinoid syndrome, despite elevated levels of serotonin, is surprising. Possible explanations with respect to patients with carcinoid tumors include a decrease in the number of serotonin receptors in the intestinal tract and the skin, or that the serotonin attaches to the receptors, but some patients have a blunted postreceptor physiological response to the serotonin.

### Diagnostic Tests

The overproduction of serotonin is estimated by measuring 5-HIAA excretion in a 24-hour urine collection. Elevated levels of serotonin in the blood are estimated by measuring serum serotonin concentration. It is frequently difficult to visualize the small primary carcinoid tumor in the submucosa of the intestine. Patients frequently have liver metastases at the time of diagnosis. These can be evaluated by computer tomography (CT) or magnetic resonance imaging (MRI) of the abdomen. Because carcinoid tumors concentrate radioactive indium-111 octreotide and iodine-131 metaiodobenzylguanidine ([$^{131}$I]MIBG), nuclear medicine scans using these radioisotopes are also used to visualize the metastatic carcinoid tumor.

### Therapy

If the carcinoid tumor is not metastatic at the time of diagnosis, the primary tumor can be surgically removed. However, in the majority of patients there is tumor involvement of the lymph nodes or liver at the time of diagnosis. Many of the patients have facial flushing and diarrhea. This can be ameliorated with the serotonin receptor antagonists cyproheptadine or methysergide. If this is not effective, the patient can receive injections of either soluble or long-acting octreotide acetate. Octreotide acetate reduces secretion of serotonin from the carcinoid tumor. If the carcinoid tumor shows progressive growth, the patients can receive chemotherapy with streptozotocin and 5-fluorouracil or etoposide and cisplatinum. Some patients have had a beneficial response to moderate doses of interferon $\alpha$. If the carcinoid tumor concentrates [$^{131}$I]MIBG, large doses of this radioactive compound can be administered.

## SUMMARY

A variety of pharmacological agents can increase or decrease the physiological or pathological effects of serotonin. Serotonin agonists such as cisapride can increase intestinal motility, and serotonin antagonists such as alosetron can ameliorate some forms of irritable bowel syndrome. Selective serotonin reuptake inhibitors have dramatically improved the treatment of patients with affective disorders. Although serotonin reuptake inhibitors have been used in the treatment of severe obesity, because of their troublesome side effects on the cardiovascular system, they have not realized their clinical potential. Serotonin antagonists have markedly decreased the severe nausea and vomiting experienced by patients who receive antineoplastic chemotherapy. Finally, serotonin is the predominant neurohormone secreted from carcinoid tumors. It is responsible for the diarrhea, carcinoid heart disease, and to some extent the facial flushing that constitute the carcinoid syndrome. For reasons not yet identified not all patients with elevated serotonin production develop carcinoid syndrome. Although there is presently no cure for carcinoid tumors once they have spread to lymph nodes and liver, effective therapy has been developed to ameliorate the symptoms of these tumors. Carcinoid tumors, which have been called cancer in slow motion by Dr. Charles Moertel, remain an important tumor model for future investigation.

## See Also the Following Articles

**Appetite • Emesis • Gastric Acid Secretion • Nausea • Obesity, Treatment of • Small Intestine, Benign and Malignant Neoplasms of the**

## Further Reading


Azmitia, E. C. (2001). Modern views on an ancient chemical: Serotonin effects on cell proliferation, maturation, and apoptosis. *Brain Res. Bull.* **56**, 413–424.

De Ponti, F., and Tonini, M. (2001). Irritable bowel syndrome: New agents targeting serotonin receptor subtypes. *Drugs* **61**, 317–332.

Feldman, J. M. (1989). Carcinoid tumors and the carcinoid syndrome. *Curr. Prob. Surg.* **26**, 834–885.

Gershon, M. D. (1999). Review article: Roles played by 5-hydroxytryptamine in the physiology of the bowel. *Aliment. Pharmacol. Ther.* **13**(Suppl. 2), 15–30.

Hoyer, D., Clark, D. E., Fozard, J. R., Hartig, P. R., Martin, G. R., Mylechrane, E. J., Sxena, P. R., and Humphrey, P. P. (1994). International union of pharmacology classification of receptors for 5-hydroxytryptamine (serotonin). *Pharmacol. Rev.* **46**, 157–203.

Lindley, C., and Blower, P. (2000). Oral serotonin type 3 receptor antagonists for prevention of chemotherapy induced emesis. *Am. J. Health Syst. Pharm.* **57**, 1685–1697.

Meguid, M. M., Fetrissov, Varima, M., Sato, T., Zhang, L., Laviano, A., and Rossi-Fanelli, F. (2000). Hypothalamic dopamine and serotonin in the regulation of food intake. *Nutrition* **16**, 843–847.

Oberg, K. (2002). Carcinoid tumors: Molecular genetics, tumor biology, and update of diagnosis and treatment. *Opin. Oncol.* **14**, 38–45.

Onaitis, M. W., Kirshbom, P. M., Hayward, T. S., Qualye, F. J., Feldman, J. M., Seigler, H. F., and Tyler, D. S. (2000). Gastrointestinal carcinoid: Characterization by site of origin and hormone production. *Ann. Surg.* **232**, 549–556.


# Sexually Transmitted Diseases


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**darkfield microscopy** The most direct method of diagnosing syphilis. The surface of the genital ulcer is first gently abraded with gauze and the serous exudate of the lesion is then expressed onto a glass slide; *Treponema pallidum* has a characteristic corkscrew appearance.

**enteritis** Infection with small intestinal symptoms such as nausea, bloating, and abdominal pain, but without sigmoidoscopic changes; can follow ingestion of material contaminated with feces.

**high-resolution anoscopy** Technique similar to cervical colposcopy; uses identical equipment (a powerful light source and binocular lenses) to allow identification and biopsy of lesions that have contributed to abnormal anal cytologic findings. Acetic acid (3%) and Lugol solution (iodine) can be used to identify human papillomavirus-infected tissue in the anal canal as well as in the cervix.

**proctitis** Inflammation that may be caused by infections of the anorectal mucosa; associated with sigmoidoscopic findings limited to the distal 15 cm of the rectum. A range of cells can be affected, from keratinized, stratified squamous epithelium in the perianal area to columnar epithelium in the rectum.

**proctocolitis** Inflammation that may be caused by infections of the rectum and colon; sigmoidoscopic findings extend proximally above 15 cm of the rectum.


**Sexually transmitted diseases in the intestinal tract include those caused by protozoa, helminths, bacteria, and viruses. Many of these diseases present acutely; others persist and may have malignant potential. Infection is commonly a direct consequence of oral genital contact, oral–anal contact, or anal receptive intercourse. Sexually transmitted enteric infections also reflect a high prevalence of carriage of intestinal pathogens, particularly in certain subpopulations, such as men who have sex with men. Preventative messages of safe sex, screening of at-risk individuals, and vaccines are important medical interventions.**


## INTRODUCTION

Sexual behavior is a major force in the transmission of bacterial, protozoan, and viral enteric diseases in adults.

With the advent of the acquired immune deficiency syndrome, a sexually transmitted disease (STD) with an important enteric mechanism of infection, emphasis on safe sex temporarily reduced the incidence of sexually transmitted enteric diseases, but has not dramatically altered the importance of sexual transmission of the specific organisms. Indeed, there is a disturbing recent trend of increasing enteric STDs, particularly among men who have sex with men (MSM) in major metropolitan areas. Furthermore, unprotected anal sex is common in other populations, such as injection drug users and heterosexual adolescents and adults of both sexes, but they are not often targeted for safe anal sex messages.

## APPROACH TO THE PATIENT

Any patient who presents with intestinal complaints and a history of high-risk sexual activity must first be considered for *human immunodeficiency virus* (HIV) testing. Concomitant with this, an approach for the diagnosis of intestinal and anorectal symptoms focuses on symptom complexes of enteritis, proctocolitis, and proctitis (Table I).

## PROTOZOAL AND HELMINTHIC INFECTIONS

### Amebiasis

The protozoa *Entamoeba histolytica* is the causative agent in intestinal amebiasis. Although most infection is asymptomatic, amebic dysentery and other extraintestinal manifestations of infection, such as liver abscess, can occur. Sexual transmission is not the predominant means of acquisition—exposure to contaminated food and water is—but individuals who practice oral–anal sex are at higher risk. Cysts are the infectious form and as little as one cyst can cause infection after ingestion. Patients usually present subacutely over 1 to 3 weeks with diarrhea, abdominal pain, and bloody stools. Fever can occur in a minority of patients. There is also a chronic form of the disease that may mimic inflammatory bowel disease. A diagnosis may be made by stool examination, but this does not distinguish between *E. histolytica* and the less pathogenic *Entamoeba dispar*. Antigen detection assays have the highest sensitivity and provide the most information but are not available in all centers. First-line treatment is metronidazole (750 mg, orally for 10 days), which acts by treating both the invading trophozoites and the intraluminal cysts. A second luminal cysticidal agent, such as paromomycin (30 mg/kg per day, orally in three divided doses for 5 to 10 days) or diiodohydroxyquin (iodoquinol) (650 mg, orally three times daily for 20 days), is usually recommended.

### Giardiasis

*Giardia lamblia*, a flagellated protozoan, is an important cause of diarrhea in the United States. Direct person-to-person transfer can occur during sex. MSM have a higher prevalence of giardiasis, with anal intercourse as a risk factor. Infection may also be acquired by contaminated food and water. Presentation is highly variable and many cases are asymptomatic. Less than 50% of those infected have acute giardiasis, which is marked by the sudden onset of watery diarrhea that is foul smelling and is associated with abdominal

**TABLE I Common Sexually Transmitted Gastrointestinal Syndromes**

| Variable | Characteristics of syndrome | | |
|---|---|---|---|
| | Proctitis | Protocolitis | Enteritis |
| Symptoms | Rectal pain, discharge, tenesmus | Proctitis symptoms plus cramps, diarrhea | Diarrhea, cramps, bloating, nausea |
| Pathogen(s) | *Neisseria gonorrhoeae, Chlamydia trachomatis, Treponema pallidum*, herpes simplex virus | *Entamoeba histolytica, Campylobacter jejuni, Shigella flexneri, C. trachomatis* (LGV[a]) | *Giardia lamblia* |
| Mode of acquisition | Receptive anal intercourse | Direct or indirect fecal–oral contact | Direct or indirect fecal–oral contact |
| Anoscopic findings | Rectal exudate ± friability | Rectal exudate, friability that may extend into the sigmoid colon | Normal |

[a] Lymphogranuloma venereum strains.

From Rompalo, A. M. (1999). Diagnosis and treatment of sexually acquired proctitis and proctocolitis: An update. *Clin. Infect. Dis.* 28(Suppl. 1), S84–S90, with permission from The University of Chicago Press.

cramps. Fever occurs in only 10% of patients. Diagnosis is usually via stool microscopy; cysts or trophozoites may be detected in 90% of cases when three stool specimens are submitted. *Giardia* antigen enzyme-linked immunoassay (ELISA) may provide a higher yield. Patients with symptomatic disease should be treated. Metronidazole (250 mg, orally three times a day for 5 days) is the preferred treatment. Albendazole is an alternative agent.

## HELMINTHS

Only helminths that do not require a period of maturation outside the host are susceptible to direct person-to-person transmission. *Enterobius* (pinworm) and *Strongyloides* species have been associated with sexual transmission. *Taenia solium* (pork tapeworm), *Taenia saginata* (beef tapeworm), and *Hymenolepsis nana* may be transmitted through oral–anal contact as well.

## BACTERIAL INFECTIONS

### Gonorrhea

Gonorrhea is a common sexually transmitted disease in the United States and an etiologic agent of pharyngitis and proctitis. It is also an important cause of urethritis in men and cervicitis in women, with sequelae of pelvic inflammatory disease and infertility. Subphrenic gonococcal infection (Fitz–Hugh–Curtis syndrome) may arise by contiguous spread from infected fallopian tubes through the peritoneal cavity. Although the early behavioral response to the HIV epidemic in MSM resulted in lower rates of gonorrhea, there has been a recent trend in increasing rates of anorectal gonorrhea in some communities. Anorectal gonorrhea, which is often asymptomatic, occurs in men and women who practice anal intercourse. Patients may present with purulent rectal discharge, constipation, tenesmus, and pain. Gonorrhea-associated pharyngitis is frequently asymptomatic, with pharyngeal exudates as the only evidence of infection. Diagnosis is usually via culture on Thayer–Martin agar. Unlike urethritis, diagnosis by gram stain is less reliable in extragenital infection. DNA amplification methods such as the ligase chain reaction (LCR) initially were approved for diagnosis of urethral gonorrhea but have promise for rectal and pharyngeal gonorrhea as well. Current treatment recommendations include third-generation cephalosporins (cefixime, 400 mg, orally, or ceftriaxone, 125 mg, intramuscularly). Fluoroquinolones are no longer recommended in some parts of the United States and other countries due to increasing microbial resistance. Coinfection with *Chlamydia* is assumed and the Centers for Disease Control and Prevention (CDC) recommend concomitant treatment. All sexual partners who have had contact with the patient in the last 60 days should be offered treatment.

### Syphilis

Syphilis is a chronic disease caused by *Treponema pallidum*. Except for perinatal transmission, virtually all cases of syphilis are acquired from sexual transmission. During sexual activity, microscopic tears enable the treponeme to invade the subcutaneous tissue, where an initial chancre develops. Secondary syphilis corresponds to the subsequent treponemia that occurs weeks to months later, despite a host immune response. The patient may then undergo an asymptomatic period called latent disease. Finally, late or tertiary disease may occur in untreated patients. The manifestations of disease are famously protean. They range from a painless chancre in primary syphilis (early disease) to central nervous system involvement and aortitis in late disease. Gastrointestinal involvement can occur at any stage of the disease, from oral and anorectal chancres in primary disease, mucocutaneous patches (oral, gastric, and rectal) and hepatitis in secondary disease, and gummatous syphilis, which can affect any organ in late disease. Diagnosis of disease is mainly by serologic testing, though the organism can also be visualized using dark-field microscopy in the early (primary and secondary) stages of disease. There are two types of serology testing. Nontreponemal tests, such as the Venereal Disease Research Laboratory (VDRL) test and the Rapid Plasma Reagin (RPR) test, are typically used for screening and the reported titer can be followed. Treponemal tests, such as the fluorescent treponemal antibody absorption (FTA-ABS) test and the microhemagglutination test for antibodies to *Treponema pallidum* (MHA-TP), are used as confirmatory tests when the screening tests are positive. Penicillin remains the drug of choice for treatment, but the choice of formulation and the duration of therapy depend on the stage of disease diagnosed. All forms of early syphilis can be treated by a single dose of benzathine penicillin G (2.4 million units, intramuscularly). This dose of benzathine penicillin G weekly for 3 weeks is the recommended treatment for syphilis of unknown stage and for late syphilis, with the exception of neurosyphilis. For neurosyphilis, intravenous penicillin G (3–4 million

units, intravenously every 4 hours for 10 to 14 days) is the regimen of choice.

### *Chlamydia*

*Chlamydia trachomatis* is the most common bacterial sexually transmitted infection in men and women. It is a rare cause of proctitis and perihepatitis. The *Chlamydia*-associated genital ulcer disease, lymphogranuloma venereum (LGV), is predominantly a disease of tropical and subtropical areas of the world and can progress to a particularly severe form of proctitis. This is associated with certain serovars in individuals who have had anal intercourse. Anorectal fibrosis, strictures, perirectal abscesses, and fistulas can be late complications in untreated disease. Outside the gastrointestinal tract, urethritis (in men and women) and cervicitis and pelvic inflammatory disease (in women) are diagnosed more frequently. Because chlamydial infections are so prevalent, serologic tests such as complement fixation or microimmunofluorescence are of limited use in confirming a causal role for *Chlamydia* in a specific symptom complex. However, an appropriate clinical presentation combined with a positive serologic test is usually adequate for a presumptive diagnosis of LGV. Serial titers demonstrating a titer rise are confirmatory. Chlamydial urethritis and cervicitis can be diagnosed by nucleic acid amplification tests (LCR or polymerase chain reaction). Culture, antigen detection tests, and genetic probe methods are alternative methods of diagnosis. Azithromycin (1 g, orally as a single dose; may not be effective in LGV) or doxycycline (100 mg, orally twice a day for 7 days; 21 days in LGV) is the treatment regimen of choice.

### *Shigella*

*Shigella* species are an important cause of diarrhea worldwide. Shigellosis is caused by ingestion of contaminated food and water or by direct person-to-person spread, including sexual transmission, perhaps because only 10 to 100 organisms are needed before infection occurs. After ingestion, organisms travel through the stomach to the small intestines and the colon. Symptoms may include the abrupt onset of fever, nausea, and crampy diarrhea, which may be watery or contain blood, mucus, and pus. Diagnosis is by culture. Ciprofloxacin (500 mg, orally twice a day for 3 days) is the treatment of choice.

### *Salmonella*

*Salmonella* species are gram-negative bacilli that cause a spectrum of disease, ranging from diarrhea and enteric fever to bacteremia, osteomyelitis, and abscesses. Most transmission is via contaminated food and water; *Salmonella* species are very rarely transmitted by sexual contact. This is possibly because as many as $10^4$ to $10^6$ organisms are required before infection. However, *Salmonella* has been implicated as a cause of enteritis in MSM.

### *Campylobacter*

*Campylobacter* species are curved, motile gram-negative rods that are one of the most common causes of acute diarrhea in the United States. Infection is typically through contaminated food and water, commonly chicken or dairy products. These organisms have also been identified as one etiology of proctocolitis in MSM.

## VIRAL INFECTIONS

### HIV

Sexual transmission accounts for most HIV acquisition worldwide. Anal intercourse is the predominant means of transmission among MSM and an important means of acquiring infection by heterosexual men and women. Patients infected with HIV often have gastrointestinal symptoms, including thrush and diarrhea. Dysphagia, odynophagia, abdominal pain, hepatobiliary disease, and anorectal disease can be common in patients with advanced disease. However, with the advent of complex combined antiretroviral and other therapies, adverse effects of antiretroviral therapy are often an important explanation for these symptoms.

### Herpes Simplex Virus

Sexual transmission of herpes simplex virus (HSV) occurs by direct skin-to-skin contact. HSV-1 typically affects the oral cavity, skin, eyes, central nervous system, and liver, whereas HSV-2 is mainly implicated in anogenital infections, though either serotype can cause infection in any location. Disease is either primary or recurrent because the virus goes into latency after initial infection. Most HSV-1 infection is asymptomatic. When diagnosed, presentation is usually sudden, with groups of painful vesicles with an erythematous base. Oral infection can present as an exudative pharyngitis in adults. Lesions may occur anywhere in the oral mucosa. In most patients, the disease is self-limited and resolves after 10–14 days. HSV-2 commonly causes anorectal disease. Initial presentation is usually more severe than recurrent disease, with fever, severe pain, and constipation. HIV-positive

patients may have severe acute, recurrent, or chronic disease, with involvement anywhere along the gastrointestinal tract, presenting as odynophagia, gastrointestinal bleeding, anorectal pain, and occasionally colitis. HSV hepatitis is a rare disease that can be caused by either serotype. Patients with HSV hepatitis are generally immunocompromised, such as transplant patients on antirejection medications and HIV-positive patients. Presentation is usually fulminant and with a high fatality rate. Diagnosis is often clinical, with confirmation by viral culture or polymerase chain reaction (PCR), which is sensitive but has limited availability. Treatment depends on whether disease is primary or recurrent, the location of infection, and the immune status of the host. Acyclovir, famciclovir, or valacyclovir is typically used to shorten the duration of symptoms, to reduce pain, and for prophylaxis, but does not reduce asymptomatic shedding and transmission. Vaccines have the potential to stem transmission of disease and reduce the frequency and severity of recurrent disease but are not yet clinically available.

### Human Herpesvirus 8

Human herpesvirus-8 (HHV-8), or Kaposi's sarcoma-associated herpesvirus (KSHV), is a novel herpesvirus identified in 1994. It is thought to be transmitted primarily through sexual contact and to be the etiologic agent of Kaposi's sarcoma (KS), body cavity-based lymphoma (a variant of non-Hodgkin's lymphoma), and perhaps multicentric Castleman's disease. The precise method of transmission is unknown but virus has been found in saliva and to a lesser extent in semen, the female genitourinary tract, the gastrointestinal tract, and the prostate. There are also reports of the virus being transmitted by organ transplantation. Diagnosis has not yet been standardized but PCR and serologic methods have been developed. Although the best treatment options for HHV-8 are still unknown, it has been observed that highly active antiretroviral therapy (HAART) is associated with regression of KS lesions.

### Human Papillomavirus

Human papillomavirus (HPV) is the most common sexually transmitted infection in the United States. It is the etiologic agent of anogenital, oral, respiratory, and skin condylomata; anal and cervical intraepithelial neoplasia; and anogenital malignancy, including the anus and the cervix. Diagnosis is frequently made by clinical appearance of exophytic warts. However, for most cervical and anal intraepithelial neoplasia, cytology is usually the first diagnostic step, followed by colposcopy or high-resolution anoscopy-directed biopsy for histopathologic confirmation. The application of acetic acid and iodine increases the sensitivity of colposcopy to detect lesions. PCR and hybrid capture assays can determine the HPV type. These tests are not used routinely in clinical practice but are currently being investigated. Treatment of warts is usually for cosmetic reasons, though occasionally they may cause symptoms and warrant removal in the anogenital, oral, and respiratory areas. High-grade anal and cervical lesions are ablated in a variety of ways to prevent invasive cancer. Low-grade disease is followed closely. Both therapeutic and preventative vaccines are currently under development.

### Hepatitis A

Hepatitis A virus (HAV) is an RNA virus transmitted via the oral–fecal route, either by ingesting contaminated food and water or by sexual transmission. Infection usually results in an acute, self-limited disease. Prodromal symptoms of malaise, nausea, vomiting, and fever lead to marked jaundice and significant elevations in aminotransferases (to over 1000 μ/liter). Only a small proportion of cases progress to fulminant disease, with an increased risk in patients with chronic hepatitis C or other underlying liver diseases. Diagnosis is by serology, with a positive serum immunoglobulin M (IgM) anti-HAV in acute infection. Treatment is mainly supportive but transplantation may be necessary in fulminant disease. For susceptible adults, preventative hepatitis A vaccine is important in at-risk populations, especially in MSM.

### Hepatitis B

Sexual transmission remains the primary mode of infection by hepatitis B virus (HBV)in the developed world. Perinatal transmission, infection during childhood, injection drug use, and transfusions are other methods of acquiring infection. Most infection is subclinical. Individuals who develop symptoms may present with malaise, fatigue, and right upper quadrant tenderness, followed by jaundice with aminotransferases values over 1000 μ/liter. Less than 1% of patients will develop fulminant disease. The rate of progression to chronic hepatitis is related to the age of infection; in adults, this is less than 5%. The diagnosis of HBV infection can also be made by serology with the detection of hepatitis B surface antigen (HBsAg). HBV DNA by PCR is often used to assess response to therapy. Treatment of acute disease is generally supportive. Selected patients

with chronic disease may benefit from lamivudine and the newer antivirals that are being developed. Preventative hepatitis B vaccines remain the best strategy for control of disease and are widely available.

## Hepatitis C

The risk of sexual transmission of hepatitis C virus (HCV) is thought to be low, but partners of patients infected with hepatitis C, MSM, and individuals with multiple sexual partners have an increased risk of infection. Most individuals have acquired infection parentally through injection drug use or via contaminated blood transfusions. However, more than 40% of newly infected patients have no identifiable risk factor. Most patients with acute infection are asymptomatic and most acute infections will become chronic. Diagnosis is by serology for detection of anti-HCV antibodies. Detection of HCV RNA by PCR is used increasingly to confirm the diagnosis and to assess response to therapy of hepatitis C. Treatment options in selected patients with chronic disease include combination therapy with pegylated interferon and ribavirin.

## See Also the Following Articles

**AIDS, Biliary Manifestations of • AIDS, Gastrointestinal Manifestations of • AIDS, Hepatic Manifestations of • *Campylobacter* • Giardiasis • Helminth Infections • Hepatitis A • Hepatitis B • Hepatitis C • Proctitis and Proctopathy • *Salmonella* • *Shigella***

## Further Reading

Centers for Disease Control (2003). Web site: http://www.cdc.gov.

Chin-Hong, P., and Palefsky, J. (2002). Natural history and clinical management of anal HPV disease in men and women infected with human immunodeficiency virus. *Clin. Infect. Dis.* 35, 1127–1134.

Martin, J. N., Ganem, D. E., Osmond, D. H., Page-Shafer, K. A., Macrae, D., and Kedes, D. H. (1998). Sexual transmission and the natural history of human herpesvirus 8 infection. *N. Engl. J. Med.* 338, 948–954.

Owen, R. L. (1998). Proctitis and sexually transmissible intestinal diseases. *In* "Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management" (M. Feldman, B. Scharschmidt, and M. Sleisenger, eds.), 6th Ed., pp. 1943–1960. W. B. Saunders, Philadelphia.

Quinn, T. C. (1986). Clinical approach to intestinal infections in homosexual men. Med. *Clin. North Am.* 70, 611–634.

Quinn, T. C., Stamm, W. E., Goodell, S. E., Mkrtichian, E., Benedetti, J., Corey, L., Schuffler, M. D., and Holmes, K. K. (1983). The polymicrobial origin of intestinal infections in homosexual men. *N. Engl. J. Med.* 309, 576–582.

Rompalo, A. M. (1999). Diagnosis and treatment of sexually acquired proctitis and proctocolitis: An update. *Clin. Infect. Dis.* 28(Suppl. 1), S84–S90.

Royce, R. A., Sena, A., Cates, W., Jr., and Cohen, M. S. (1997). Sexual transmission of HIV. *N. Engl. J. Med.* 336, 1072–1078.

# *Shigella*

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**bacillary dysentery** Diarrheal illness caused by bacteria belonging to the genus *Shigella*.

**pathogenicity island** Mobile genetic element, often encoding virulence genes; found in many pathogenic bacteria and propagated by horizontal gene transfer.

**type III secretion apparatus** Macromolecular structure on the surface of some gram-negative pathogenic bacteria; required for the direct translocation of bacterial virulence proteins into the cytosol of the host cell.

**Bacillary dysentery is a major cause of morbidity and mortality throughout the world, especially in infants and young children in developing countries. *Shigella* spp. are the causative agents of this disease. Bacillary dysentery is a major public health problem in light of the highly contagious nature of this infection, the emergence of multiple antibiotic resistance, and the lack of an effective vaccine.**

## MICROBIOLOGY

*Shigella* spp. belong to the family Enterobacteriaceae and are closely related to *Escherichia coli*. They are gram-negative, nonmotile, and nonencapsulated bacilli. The four species, *Shigella dysenteriae, Shigella flexneri, Shigella boydii*, and *Shigella sonnei*, are differentiated by lipopolysaccharide (LPS) antigens (A, B, C, and D, respectively), biochemical properties, and phage or colicin susceptibility. Different serotypes subdivide each species.

### Virulence Factors

The infectivity of *Shigella* spp. is dependent on bacterial entry into host cells. The invasive phenotype depends on the presence of a large plasmid; strains that lack this plasmid are no longer invasive or virulent. Proteins encoded by genes contained within a pathogenicity island in the plasmid induce bacterial entry into host cells. These proteins form a type III secretion apparatus that transfers a number of virulence proteins directly from the bacteria into the host cytosol, to induce a form of macropinocytosis that effectuates bacterial invasion. Once inside the cell, *Shigella* moves within the cytosol and from cell to cell using actin-based motility (see Fig. 1).

**FIGURE 1** *Shigella* is able to recruit host cell actin to form an actin comet tail, necessary for intra- and intercellular propulsion. Here, primary cultures of mouse enterocytes are infected by *S. flexneri*, which express green fluorescent protein (GFP); the bacterial-associated actin comet tails are stained with phalloidin/tetraethylrhodamine isothiocyanate. Micrograph courtesy of Drs. Rafika Athman and Sylvie Robine, Institut Curie, Paris, France.

The virulence of *S. dysenteriae* type 1 is compounded by the expression of a potent cytotoxin, called shiga toxin. This toxin is an AB subunit toxin that mediates cell death through inhibition of protein synthesis. Shiga toxin effectively targets those cells that express globotriaosyl ceramide ($Gb_3$), which is the receptor for the toxin. Shiga toxin is important for the development of hemolytic uremic syndrome (HUS; see later).

### Immune Response

*Shigella* infection induces local innate immune defense systems, including the recruitment of bactericidal neutrophils to the infected site. In terms of adaptive immunity, the production of secretory immunoglobulin (IgA) directed against the O antigen of

 

lipopolysaccharide has been shown to be protective in animal models of shigellosis. However, this immunity is relatively short-lived and serotype specific, which, together, greatly hampers the successful design of effective vaccine candidates.

## EPIDEMIOLOGY

*Shigella* is exclusively a human pathogen and is transmitted by the fecal–oral route through close personal contact or by way of infected food or water. In contrast to the other enteropathogens, *Shigella* is highly contagious; as few as 200 *S. flexneri* organisms are sufficient to induce diarrhea and fever. For comparison, similar symptoms and a similar attack rate due to *Salmonella* require an inoculum 100 times greater.

In developed countries, shigellosis causes disease primarily in custodial institutions, nursing homes, or day-care centers. Each year, 15,000 cases of shigellosis, essentially due to *S. sonnei*, are reported in the United States. Shigellosis is common in developing countries where poverty, overcrowding, poor hygiene, and malnutrition prevail. The World Health Organization (WHO) estimates that shigellosis causes 160 million cases of diarrhea each year and 1.1 million deaths worldwide. *Shigella flexneri*, and, to a lesser extent, *S. sonnei*, are responsible for endemic disease whereas epidemic outbreaks are due to *S. dysenteriae* type 1. *Shigella* infection is a disease essentially of children less than 5 years of age.

## DIAGNOSIS

### Clinical Diagnosis

After an asymptomatic incubation period of 1–7 days, shigellosis begins suddenly with abdominal pain, vomiting, anorexia, and fever. Soon after, watery diarrhea develops; this becomes bloody in 50% of patients and presents with tenesmus and abdominal cramps. These intestinal contractions may induce rectal prolapse. In healthy volunteers without antibiotic treatment, diarrhea abates by the seventh day, although stool cultures remain positive for an average of 27 days.

### Paraclinical Exams

Leukocytosis is often mild but can become leukemoid (more than 50 g/liter). The examination of fresh stool stained by methylene blue can reveal significant leukocyte counts, consistent with a nonspecific invasive bacterial pathogen. Stool culture is the most informative exam.

### Complications

Complications occur more frequently among very young or malnourished children in developing countries. During the acute phase, metabolic disorders such as hypoglycemia and hyponatremia can be observed. Dehydration and septicemia are rare during shigellosis. Among digestive complications, toxic megacolon and intestinal perforation are more frequently observed with *S. dysenteriae* type 1, which can result in a high mortality rate. Neurological complications can also occur. For example, seizures may occur in children before fever appears and *S. flexneri* has been documented to cause encephalopathy without hypoglycemia and bacterial meningitis.

*Shigella* infection can induce protein-losing enteropathy, which may be responsible for growth retardation in children. Immune deregulation may cause Reiter's syndrome in HLA-B27 patients in association with arthritis, urethritis, and conjunctivitis. HUS can be a complication following infection with *S. dysenteriae* type 1, due to shiga toxin. HUS is characterized by acute hemolytic anemia, thrombocytopenia, and renal failure. Both hemolytic uremic and Reiter's syndromes can occur during the convalescence phase after diarrhea has subsided.

## TREATMENT

### Curative

Except for symptomatic treatment to control hypoglycemia, hyponatremia, or seizures, the main therapy of shigellosis is antibiotics. In developed countries, a majority of *Shigella* infections are mild and self-limited and often do not require antibiotic treatment. However, in severe shigellosis, several antibiotics have been demonstrated to reduce the duration of the disease and eliminate *Shigella* from the stool. However, *Shigella* spp. have acquired resistance to a number of antibiotics, including tetracycline, ampicillin, trimethoprim-sulfamethoxazole, and fluoroquinolone. The choice of antibiotic should be adapted to the local epidemiology of resistance and to the results of the stool culture, if available.

### Preventive

Person-to-person transmission of *Shigella* can be reduced by hand washing with soap, segregating the ill persons, and separating eating areas from care zones. Increased sanitary conditions in developing countries will certainly decrease the incidence of this

infection. Efficient vaccines are not currently available; however, the development of a multivalent vaccine effective against the most prevalent species of *Shigella* is a major priority for the WHO.

## See Also the Following Articles

**Bacterial Toxins • Foodborne Diseases • Food Poisoning • Food Safety • *Salmonella* • *Yersinia***

## Further Reading

Kotloff, K. L., Winickoff, J. P., Ivanoff, B., Clemens, J. D., Swerdlow, D. L., and Sansonetti, P. J. (1999). Global burden of *Shigella* infections: Implications for vaccine development and implementation of control strategies. *Bull. World Health Organ* 77(8), 651–666.

Philpott, D. J., Edgeworth, J. D., and Sansonetti, P. J. (2000). The pathogenesis of *Shigella flexneri* infection: Lessons from *in vitro* and *in vivo* studies. *Philos. Trans. R. Soc. Lond., B, Biol. Sci.* 355(1397), 575–586.

# Short Bowel Syndrome

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**cholerrheic diarrhea** Resulting from the presence of malabsorbed bile acids.

**dual-energy X-ray absorptiometry** Noninvasive technique used to assess body composition, specifically bone and soft tissue.

**hyperosmolar fluid** Highly concentrated solution that contains several osmotically active particles, such as glucose or sodium.

**isotonic fluid** Solution that contains electrolytes, nonelectrolytes, or a combination of both, having the same concentration as the solution to which it is being compared (e.g., blood).

**polymeric** Containing complete proteins, carbohydrates, and fat rather than predigested substances.

**probiotics** Live microbial supplements; used to reestablish normal intestinal flora.

**secretory diarrhea** Resulting from the excessive secretion of water and electrolytes into the lumen of the bowel; persists or slows only partially after 24–48 hours of fasting.

**Short bowel syndrome is a relatively rare, but devastating, clinical problem characterized by severe diarrhea, malabsorption, fluid and electrolyte abnormalities, and progressive malnourishment resulting from the loss of functional small bowel absorptive surface area. Although the care of patients has often focused on minimizing symptoms and the appropriate replacement of fluid and nutrient losses, therapeutic advancements and comprehensive treatment programs offer new options.**

## ANATOMIC AND PHYSIOLOGIC FACTORS

Estimates of adult small intestinal length vary from 12 to 20 feet (or 365 to 600 cm). Length has been found to vary with the height and sex of the individual, being slightly longer in men. The duodenum is the first segment of the small bowel and measures approximately 10 inches (25 cm). The remainder of the small bowel is composed of the jejunum and ileum; with the more proximal jejunum comprising approximately two-fifths of this length and the ileum comprising three-fifths. Throughout the small bowel, the mucosa is composed of convoluted folds containing fingerlike projections (villi) that protrude into the lumen. These villi are further augmented by the presence of microvilli (approximately $2 \times 10^8$ per square centimeter) on the outer, or brush border, region of the epithelial cells, contributing to the enormous total absorptive surface area of the adult small intestine.

Many substances are absorbed throughout the length of the small intestine, but certain nutrients

tend to be absorbed more in one region than another. The proximal intestine is the major site for the absorption of iron, calcium, water-soluble vitamins, monoglycerides, and simple fatty acids. Sugars are absorbed in the proximal and midintestine. Amino acids appear to be absorbed primarily in the midintestine or the jejunum, although some absorption also occurs in the proximal and distal segments. Intestinal intubation studies have shown that the absorption of carbohydrate, protein, and simple fatty acids is primarily complete within the first 100 cm of the jejunum. The distal small bowel (ileum) appears to be the major absorptive area for vitamin $B_{12}$ and for bile salts. The bile salts play an important role in the absorption of fat (or triglycerides) and fat-soluble vitamins. Although the colon is an important site for the absorption of water and electrolytes, the small bowel also plays an important role. Under normal circumstances, the intestine is presented with ~2000 ml of ingested fluids and ~7000 ml of secretions from the gastrointestinal tract and associated glands. Approximately 98% of this fluid is reabsorbed (with estimates of ~5500 ml in the jejunum, ~2000 ml in the ileum, and ~1300 ml in the colon), with a daily fluid loss of ~200 ml in the stool.

## ETIOLOGY

Significant loss or dysfunction of the intestinal absorptive surface area results in the short bowel syndrome. This syndrome is most often the result of extensive resection of the small bowel due to infarction of the mesenteric vessels, intestinal volvulus, trauma, malignancy, congenital abnormalities, or complications of Crohn's disease. Less often the defect is functional, rather than anatomical, such as in the case of radiation enteritis or severe inflammatory bowel disease.

## CLINICAL DESCRIPTION

Short bowel syndrome is a complex of symptoms consisting of severe diarrhea and macro- and micronutrient malabsorption resulting in suboptimal hydration, electrolyte disturbances, progressive weight loss, and nutrient deficiencies. These problems can be physically debilitating and socially incapacitating and can require aggressive interventions that can contribute to a myriad of complications. The severity of the short bowel syndrome is determined by a number of factors, including (1) the degree to which the bowel has adapted following resection, (2) the length, location, and health of the remaining small bowel, and (3) the presence or absence of the colon.

## FACTORS INFLUENCING SEVERITY

### Bowel Adaptation

The process of bowel adaptation is characterized by an elongation and dilation of the remnant bowel, and in animal models an increase in villus height, crypt depth, cell proliferation, and enzyme activity. These alterations in bowel morphology and function are thought to be mediated in part by factors extrinsic to the gastrointestinal tract (hormones, growth factors, prostaglandins, etc.), by local factors brought into play by the provision of oral or enteral feedings (e.g., enteric hormones, pancreatic–biliary secretions), and by exposure of the mucosa to specific nutrients or nonnutrient components of the diet (e.g., short chain fatty acids, glutamine, fiber). In animals, the absence of luminal nutrients inhibits intestinal hyperplasia even when necessary amounts of calories are provided parenterally. Clinically, bowel adaptation is marked by gradual improvements in symptoms—a decrease in diarrhea and an improved tolerance to and absorption of enteral nutrients. Although the process of bowel adaptation begins almost immediately following extensive resection, the process may not be maximized for 1–2+ years.

### Length, Location, and Health of Remnant Bowel

Because of the tremendous length of the small intestine and its ability to adapt and compensate for the loss of absorptive surface area, relatively normal intestinal function could be expected after resection of approximately one-third of the bowel. However, resections necessitating the removal of greater than 50% of the small bowel are associated with metabolic complications and often require more aggressive interventions.

In addition to remnant length, the site of the resection influences the clinical sequelae. Loss of the distal small intestine is often more devastating than loss of the more proximal bowel. If the jejunum is removed, the ileum often adapts and assumes its absorptive functions. However, because of the unique functions of the ileum, particularly bile salt absorption, loss of even 100 cm or less of ileum can result in watery, cholerrheic diarrhea. When more than 100 cm of ileum is resected, bile salt loss in the stool can be considerable. Consequently, fewer bile salts are available, limiting the absorption of fat and fat-soluble vitamins, with resultant steatorrhea. The unabsorbed free fatty acids bind with calcium, magnesium, and zinc, forming insoluble intraluminal soaps. The prolonged malabsorption of these substances necessitates supplementation to avoid deficiency states and related metabolic complications. The formation of

unabsorbable calcium soaps prevents intraluminal calcium from binding to dietary oxalates. If colon is present, the unbound oxalates pass to the colon, where they are reabsorbed and subsequently excreted in the urine. A prolonged state of hyperoxaluria renders the patient prone to the development of calcium oxalate nephrolithiasis. An additional factor influencing calcium absorption is a reduction in serum 25-hydroxy vitamin D levels, which can be related to the loss of ileal surface area and the associated fat and fat-soluble vitamin malabsorption. Prolonged suboptimal levels of calcium and vitamin D are thought to contribute to the bone disease that can accompany the short bowel syndrome.

In addition to the absorption of fat and fat-soluble vitamins, the ileum and the colon have a greater ability than the jejunum to conserve salt and water. In addition, the ileum and colon have a marked effect on slowing intestinal transit. Consequently, resections involving only jejunum often result in very little diarrhea, because the remaining ileum and colon can accommodate the fluid and electrolyte load. In contrast, following ileal resections, the colon receives a large, relatively isotonic fluid load. However, the presence of unabsorbed bile salts and free fatty acids can alter the tonicity of the luminal contents and produce a secretory state within the colon. Although the colon can handle ~5 liters of fluid per day, volumes in excess of this can result in diarrhea and excessive fluid and electrolyte losses. For patients with jejunostomies (no functional ileum or colon), the remaining jejunum is often unable to concentrate the luminal contents, and water and sodium loss is often severe.

The health of the remnant bowel influences the severity of the symptoms confronting the patient with short bowel syndrome. Disease (e.g., Crohn's) or damage (e.g., radiation injury) can impair the functioning capacity of the remaining bowel, rendering these patients to more pronounced symptoms and long-term complications.

### Presence or Absence of Colon

In addition to the colon's important role in the absorption of fluid and electrolytes, it plays a unique role for patients with short bowel syndrome. Bacteria within the colon ferment malabsorbed carbohydrate (and to a lesser extent protein) into short-chain fatty acids, which can then be utilized for energy. Thus, for patients with short bowel, the presence of the colon is typically a good predictor of a more favorable outcome and less dependency on parenteral support. The minimal amounts of small bowel required to sustain a patient without parenteral support have been estimated to be approximately 50–70 cm, when the segment is anastomosed to functional colon, but 110–150 cm if no colon is present. These estimates assume that the remnant small bowel and colon are healthy, adequate adaptation has occurred, and the patient has received appropriate medical and nutritional care.

## MEDICAL AND NUTRITIONAL MANAGEMENT

The primary short- and long-term objectives of standard medical and nutritional management of patients with short bowel syndrome should be (1) to enhance bowel adaptation and compensation, (2) to improve absorption and reduce diarrhea, (3) to replace nutrient and fluid losses appropriately, and (4) to minimize and/or avoid long-term complications.

### Acute Postoperative Period

The immediate postoperative phase following extensive intestinal resection is characterized by massive diarrhea and fluid and electrolyte disturbances. During this time, aggressive replacement of fluid and electrolytes is required. Calorie and nutrient requirements are met via parenteral nutrition (PN) and should be prescribed according to previously published guidelines. Very small amounts of luminal nutrition should be initiated as early as possible for the purpose of encouraging bowel adaptation. The composition of the diet should be based on the presence or absence of colon, with the quantity of fat, carbohydrate, and protein evenly distributed throughout the day. Simple sugars (particularly sucrose, fructose, and lactose) and hyperosmolar beverages should be avoided. Oral rehydration solutions can be trialed. If the patient is unable to eat, a polymeric, isotonic liquid formula should be utilized. Initially, the quantity of the feeding should be restricted (e.g., $\leq$ 500 ml per 24-hour period) to avoid further exacerbation of diarrhea. An antimotility agent should be initiated, and antinausea medication utilized, if indicated. Due to acid hypersecretion following resection, antacid therapy should be started. If either secretory or cholerrheic diarrhea is documented, additional antisecretory medication can be considered (Table 1). This initial postoperative phase may last for several weeks or even months, depending on the extent of the resection.

### Long-Term Management

The second phase following extensive resection is marked by a decrease in diarrhea. The increased

TABLE I Frequently Utilized Medications

| Indication | Medication | Dose[a] |
|---|---|---|
| Rapid transit | Loperamide | 2 mg po qid |
| | Atropine sulfate | 2.5 mg po qid |
| | Opium tincture | 0.25–1.0 ml po qid |
| Secretory diarrhea | Octreotide | 50–150 μg sc tid |
| Cholerrheic diarrhea | Cholestyramine | 4 g po bid–qid |
| Acid hypersecretion | | |
| H2 receptor antagonists | Ranitidine | 150 mg po bid or 150 mg iv qd |
| | Famotidine | 20 mg po bid or 40 mg iv qd |
| Proton pump inhibitors | Omeprazole | 20 mg po bid |
| | Lansoprazole | 30 mg po bid |
| Antinausea | Compazine | 5–10 mg po tid–qid |
| | Zofran | 10 mg iv qd–tid |
| Bacterial overgrowth | Metronidazole | 250 mg po tid[b] |
| | Tetracycline | 250 mg po qid[b] |
| | Ciprofloxin | 500 mg po qd–bid[b] |

[a] For adult patients. Abbreviations: po, periorbital; qid, quater in die (four times daily); sc, subcutaneous; tid, ter in die (three times daily); bid, bis in die (twice daily); iv, intravenous; qd, quaque die (once daily).

[b] Typically administered for 10–14 days.

adaptation is accompanied by improvements in nutrient absorption. Although the composition of the oral diet continues to be based on the presence or absence of colon, the volume of food and fluid is liberalized. Parenteral support is gradually reduced and medications are adjusted, as indicated. Following extensive resection, it can take up to 1–2+ years before maximal adaptation is achieved, and during this time the overall treatment plan may need to be adjusted multiple times. Some patients with short bowel syndrome progress to a third phase, one of full adaptation, which is marked by the achievement of positive nutritional balance via oral or enteral nutrition alone. For these patients, as well as those who remain dependent on parenteral support, it is critical that they be monitored periodically to minimize the risk of potential complications associated with short bowel syndrome and/or their long-term need for PN. Recommendations for routine monitoring are provided in Table II.

## POTENTIAL LONG-TERM PROBLEMS

### Catheter-Related Complications

For those patients with short bowel syndrome that do require long-term PN, catheter-related complications, including catheter occlusion (due to thrombosis) and catheter-related infections, are the most common problem. Prevention of catheter occlusion remains a clinical challenge, because the cause can be

TABLE II Guidelines for Long-Term Monitoring

| Parameter | Baseline | Monthly | Semiannual | Annual |
|---|---|---|---|---|
| Weight | X | X | X | X |
| Skeletal muscle mass[a] | X | | X | X |
| Electrolytes | X | X | X | X |
| Vitamin and trace elements[b] | X | | X | X |
| Essential fatty acid profile | X | | X | X |
| Liver function panel[c] | X | X | X | X |
| Kidney function[d] | X | | X | X |
| Bone health[e] | X | | | X |

[a] Assessed by creatinine height index.

[b] Vitamin and mineral profile to include vitamins A, C, D (25-hydroxy), E, and $B_{12}$, and folic acid, zinc, selenium, ferritin, and prothrombin.

[c] Liver function panel should include total bilirubin, alkaline phosphatase, serum glutamic oxaloacetic transaminase, and serum glutamic pyruvic transaminase.

[d] Assessed by 24-hour creatinine clearance.

[e] Assessed by dual-energy X-ray absorptiometry.

multifactorial. Efforts to reduce the incidence of septic complications focus on the use of aseptic techniques in catheter placement and maintenance and in solution preparation and administration.

## Liver Dysfunction

Although the use of PN may result in altered liver function tests as soon as 1–2 weeks after therapy has been initiated, liver dysfunction is more frequently thought to be a long-term complication. Patients with the shortest residual intestine, particularly those without functioning remnant colon, are at greatest risk of developing eventual liver failure, suggesting that the degree of malabsorption and/or the level of dependence on parenteral nutrition are the likely causes of the dysfunction. Although nutrient deficiencies (e.g., choline, carnitine, glutamine, vitamin E, taurine) and toxicities (e.g., manganese) have been suggested as potential causes of liver dysfunction, dextrose overfeeding, lipid overload, and bacterial overgrowth are more typically associated with the abnormalities. To prevent PN-associated liver disease, carbohydrate overfeeding and the excessive use of lipid emulsion should be avoided, PN should be cycled, oral intake encouraged, and episodes of bacterial overgrowth appropriately treated and managed.

## Metabolic Bone Disease

Patients with short bowel syndrome are at risk of developing metabolic bone disease, with the two most common forms being osteoporosis and osteomalacia. In addition to chronic abnormalities in calcium and vitamin D homeostasis due to impaired nutrient absorption, factors such as chronic metabolic acidosis, the need for long-term PN, prolonged periods of inactivity, and limited sun exposure may further contribute to the problem. Efforts to minimize risk of progressive bone loss should include appropriate vitamin D and calcium supplementation and, if appropriate, sunlight exposure and an exercise regimen. Chronic acidosis should be corrected and the use of PN minimized, if possible. Dual-energy X-ray absorptiometry (DEXA) provides a noninvasive method to assess bone mineral density and should be used as a screening device for patients with short bowel syndrome.

## Nutrient Deficiencies

Vitamin, mineral, and essential fatty acid deficiencies are common in patients with short bowel syndrome. As previously mentioned, the location and the extent of intestinal resection impacts on the incidence and severity. Deficiencies can occur despite the use of routine supplementation, thus periodic monitoring is recommended (Table II). When deficiencies are identified, they should be repleted (Table III) to avoid potentially debilitating complications.

## Other Problems

Bacterial overgrowth and D-lactic acidosis are additional problems that may occur in patients with short bowel syndrome. Bacterial overgrowth is an abnormal proliferation of bacteria; changes in intestinal flora can be induced by alterations in intestinal motility and in diet (e.g., increased intake of simple carbohydrates) and/or the need for antibiotic therapy. Overgrowth of

TABLE III Guidelines for Nutrient Repletion

| Nutrient deficiency | Recommended repletion dosages[a] |
|---|---|
| Vitamin A[b] | po, 10,000–50,000 IU for 1 month; iv, 50,000–100,000 IU for 1–3 days |
| Vitamin $B_{12}$ | im, 100–1000 μg daily for 1–2 weeks to replace body stores |
| Vitamin C | po, 250–500 mg qd–bid |
| Vitamin D[c] | po, 50,000 IU daily for 1 month; im, 500,000 IU in 1–2 injections |
| Vitamin E | po, 400 IU qd–tid |
| Vitamin K[d] | po, 5–20 mg qd; iv or sc, 2.5–10 mg and monitor levels |
| Iron | po, 27–38 mg of elemental iron tid |
| Zinc | po, 50 mg of elemental zinc qd–bid |
| Selenium | po, 50–100 μg qd; iv, 20–60 μg |
| Magnesium[e] | po, 200–600 mg qd; iv or im, 1–2 g if levels are less than 1.0 mEq/liter |
| Essential fatty acids | po, 1–3 tablespoons of safflower and/or flaxseed oil; iv, 250 ml of 20% lipid in 12 doses |

[a] For adult patients. Abbreviations: po, periorbital; qd, quaque die (once daily); sc, subcutaneous; tid, ter in die (three times daily); bid, bis in die (twice daily); iv, intravenous.

[b] As retinol.

[c] As ergocalciferol.

[d] As phytonadione.

[e] As magnesium glycinate.

pathogenic bacteria has the potential to increase diarrhea and to compete with vitamins (e.g., $B_{12}$) and other nutrients. Treatment usually consists of a 10- to 14-day course of oral antibiotics (Table I) and a probiotic to repopulate the intestinal flora.

Bacterial fermentation of unabsorbed sugars can cause increased D-lactate production in the colon in some patients. These fermenting organisms can lead to D-lactic acidosis, with related neurologic impairment, including confusion, somnolence, unsteady gait, and lethargy. A specific D-lactate level is used to confirm the diagnosis. Treatment includes intravenous fluids and administration of antibiotics to reduce colonic bacterial mass. Patients who may be susceptible to D-lactic acidosis should be strongly encouraged to avoid refined sugars and to decrease their total carbohydrate intake.

Depression and narcotic dependency are additional problems that may confront the patient with short bowel syndrome. These problems should be addressed and appropriate treatment and support provided.

## ADDITIONAL TREATMENT OPTIONS

In addition to the use of approved medications and appropriate oral/enteral and parenteral nutrition regimens, other treatment options are being explored and/or utilized. These options include the use of growth factors, nontransplant surgical procedures, and intestinal transplantation.

### Growth Factors

Specific growth factors (e.g., growth hormone, glucagon-like peptide-2) have been proposed as potential adjuncts to the standard treatment of patients with short bowel syndrome. Their ability to augment bowel function and/or morphology and thereby reduce PN requirements is the focus of much research. Preliminary studies have produced conflicting results, but results from larger trials are anticipated to help clarify some of the controversy over this therapeutic approach.

### Nontransplant Surgical Procedures

In an attempt to increase the absorptive surface area and to minimize problems of bacterial overgrowth, intestinal lengthening procedures have been proposed for some patients with short bowel syndrome. This technically challenging procedure has been reported to yield favorable results in some patients, particularly those with dilated remnants. The procedure has primarily been utilized in children and clinical experience is limited to a small series in a few centers. For patients with longer remnants, reversal of intestinal segments is intended to slow intestinal transit by the interruption of normal peristalsis and the introduction of retrograde motility. Prolongation of intestinal transit and the associated improvement in nutrient absorption have resulted in some patients regaining enteral autonomy or experiencing a reduction in PN requirements. Although some authors report lasting benefit, others report only short-term success. As with all procedures, the potential benefits need to be weighed against the potential risks.

### Intestinal Transplantation

Intestinal transplantation has become a treatment option for those patients who develop life-threatening complications associated with long-term dependence on PN. An international registry has tracked the world experience on this procedure and reports indicate that the 1-year graft/patient survival rate for transplants performed after 1995 is 55/69% for intestinal grafts, 63/66% for those who undergo a transplant of both the small bowel and liver, and 63/63% for those who undergo multivisceral grafts. Despite such aggressive intervention, approximately one-quarter of the survivors still required some parenteral support. This procedure is performed more commonly in children and teenagers than in adult patients.

## INTESTINAL REHABILITATION

Comprehensive treatment programs for patients with short bowel syndrome have been developed over the past decade in specialized centers that have the opportunity to care for large numbers of patients. Well-defined protocols and the experienced clinical teams allow standard therapeutic interventions to be optimized. Interventions often include daily monitoring and adjustments in nutritional and medication regimens, comprehensive education and behavior modification programs, and long-term monitoring. If indicated, other therapeutic approaches (e.g., the use of growth factors, and nontransplant surgical interventions) may be utilized. The intent of intestinal rehabilitation is to improve the functioning capacity of the remnant bowel with the goal of avoiding significant complications or the need for intestinal transplantation.

### See Also the Following Articles

Bacterial Overgrowth • Colonic Absorption and Secretion • Diarrhea • Malabsorption • Parenteral Nutrition • Short

**Bowel Syndrome and Intestinal Transplantation, Pediatric • Small Bowel Transplantation • Small Intestine, Absorption and Secretion**

## Further Reading

American Society for Parenteral and Enteral Nutrition (ASPEN). (2002). Board of Directors and the Clinical Guidelines Task Force. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. *J. Parenter. Enteral Nutr.* 26, 1SA–138SA.

Buchman, A. (2002). Total parenteral nutrition-associated liver disease. *J. Parenter. Enteral Nutr.* 26, S43–S48.

Byrne, T., Veglia, L., Camelio, M., Cox, S., Anderson, S., Wilson, J., and Bennett, H. (2000). Beyond the prescription: Optimizing the diet of patients with short bowel syndrome. *Nutr. Clin. Practice* 15, 306–311.

Grant, D. (1996). Current results of intestinal transplantation. The International Intestinal Transplant Registry. *Lancet* 347, 1801–1803.

Grant, J. (2002). Recognition, prevention, and treatment of home total parenteral nutrition central venous access complications. *J. Parenter. Enteral Nutr.* 26, S21–S28.

Seidner, D. (2002). Parenteral nutrition-associated metabolic bone disease. *J. Parenter. Enteral Nutr.* 26, S37–S42.

Tavakkolizadeh, A., and Whang, E. (2002). Understanding and augmenting human intestinal adaptation: A call for more clinical research. *J. Parenter. Enteral Nutr.* 26, 251–255.

Thompson, J., and Langnas, A. (1999). Surgical approaches to improving intestinal function in the short-bowel syndrome. *Arch. Surg.* 134, 706–709.

# Short Bowel Syndrome and Intestinal Transplantation, Pediatric

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**adaptation** Enhancement of the intestinal structure and function to compensate for loss of small bowel length.

**elemental formulas** Solutions composed of individual amino acids, containing no whole proteins; used primarily for rapid absorption and reduction of allergic potential.

**intestinal lengthening** Surgical procedure in which the dilated small intestinal diameter is halved and joined end to end.

**rejection** Immune reaction of a transplant recipient to foreign tissues (antigens) after allograft transplantation, with production of antibodies and ultimate destruction of the transplanted organ.

**short bowel syndrome** Clinical state following bowel resection leading to malabsorption of nutrients, fluids, and/or electrolytes.

**small bowel bacterial overgrowth** Excess bacterial counts in any area of the small bowel, usually greater than $10^{10}$ colony-forming units/ml.

**total parenteral nutrition** Provision of complete nutrition via the intravenous route.

**transplantation** Transfer of living organs from one individual to another.

**tropic hormones** Play a role in stimulating bowel adaptation by encouraging intestinal villous growth and in regulating intestinal motility.

**Quantification of an anatomical definition of short bowel syndrome after surgical resection has been attempted. No consistent definition can be established because children with as little as a few centimeters of small intestine have been successfully weaned from parenteral nutrition whereas some children with longer segments of bowel have succumbed. In adults, it is generally agreed that less than 100 cm of remaining small bowel constitutes short bowel syndrome. A more practical definition focuses on the functional state of the remaining gastrointestinal tract, whereby short bowel syndrome exists when malabsorption of nutrients, fluids, and/or electrolytes occurs in the presence of any intestinal loss.**

## INTRODUCTION

Short bowel syndrome, although not common in pediatrics, remains a continuous challenge to those involved

in the care of children with this syndrome. Advances in neonatology, pediatric surgery, and intestinal feeding practices have facilitated survival of these children but enhancement of growth and development along with the avoidance of therapy-related complications present ongoing challenges.

Enteral nutrition is now the mainstay of therapy for children with extensive resections resulting in short bowel syndrome. Parenteral nutrition is required initially while the functional capacity of the small intestine is maximized. The practice of parenteral nutrition has become very sophisticated, with minimal complications occurring in patients managed by teams experienced in such therapy. Death from complications of short bowel syndrome therapy is infrequent because intestinal and liver transplantation procedures have become increasingly more reliable.

## ETIOLOGY

Although congenital short bowel syndrome does occur, most cases of short bowel syndrome in children occur following intestinal resection in previously anatomically normal infants. Typically, small bowel resection is performed to treat events occurring in the ileum and colon; however, varying degrees of jejunal resection may also be required. Table I lists the common etiologies of short bowel syndrome in both infants and older children. Congenital anomalies resulting in short bowel syndrome include intestinal atresias, which may occur anywhere in the intestine and can be either isolated or multiple. Most infants with short bowel syndrome have undergone resection due to necrotizing enterocolitis.

## INTESTINAL PHYSIOLOGY

The embryonic midgut is the origin of the small intestine, which begins rapid growth at the end of the fifth week of gestation. Intestinal lengthening exceeds the rate of growth of the embryonic body and, therefore, it must grow outside the abdomen until the tenth week. The average intestinal length at 40 weeks of gestation is 200–250 cm. Mean adult small intestinal length is approximately 500–600 cm, with primary increases in length occurring in early childhood.

TABLE I Conditions Leading to Short Bowel Syndrome

| Infants | Children |
|---|---|
| Congenital short bowel | Malignancy/tumors |
| Intestinal atresias | Radiation enteritis |
| Gastroschisis | Crohn's disease |
| Apple peel/Christmas tree deformity | Mesenteric vascular occlusion |
| Hirschsprung's disease involving ileum and colon | Trauma |
| Necrotizing enterocolitis | Chronic pseudo-obstruction |
| Volvulus | |

The most obvious change in short bowel syndrome is the loss of overall absorptive surface area. The inherent characteristics of the remaining intestine are, however, critical in determining the overall prognosis. Most commonly, there is retention of the jejunum with part of the colon. The jejunal epithelium differs significantly from that of the ileum in that the latter contains the specific transporters for bile acids and vitamin $B_{12}$. The intestinal villi create a large surface area for nutrient absorption, with most carbohydrate, protein, and water-soluble vitamins being absorbed in the proximal small intestine. Fat absorption occurs over a much larger proportion of the whole small intestine. The jejunum also has a higher concentration of enzymes and other carrier proteins, making it capable of enhanced absorptive function after distal intestinal resection.

Normally, a rapid infusion of hyperosmolar substances into the upper jejunum will result in an influx of fluid from the plasma to the lumen to equalize the osmotic differences. Reabsorption will then occur distally if the load can be absorbed. Otherwise, diarrhea ensues. In short bowel syndrome, this compensating mechanism is altered. The presence of the colon after small bowel resection provides for sodium and short-chain fatty acid absorption. Loss of the colon generally worsens the prognosis of short bowel syndrome. However, the presence of malabsorbed long-chain fats and bile acids in the colon may worsen watery diarrhea and increase oxalate absorption, with subsequent development of oxalate renal stones.

The ileum generally provides less absorptive function than the jejunum but is rapidly recruited to enhance nutrient absorption if digestive loads are large. Resection of a large portion of the ileum will result in bile salt malabsorption (with subsequent fat-soluble vitamin malabsorption) and vitamin $B_{12}$ deficiency because the jejunum cannot compensate for the loss of the appropriate receptors. The ileocecal valve plays an important role in preventing bacterial flux from the large bowel into the small bowel. The valve also is important for regulating intestinal transit. Its presence was once thought to be key to establishing enteral nutrition and weaning the pediatric patient from parenteral nutrition. In practice, however, other factors such as the length of resection and the hormonal and neural responses to enteral nutrients are also important. In fact, any factors

that result in slower transit may enhance the risk of bacterial overgrowth.

Intestinal adaptation begins rapidly after the initial intestinal resection. In addition, the small intestine appears to undergo enhanced hyperplasia with greater nutrient exposure, although data studies in human are conflicting. Villus hypertrophy occurs by several mechanisms, including neural influences, direct nutrient contact with the enterocytes, and release of tropic substances from the stomach, liver, pancreas, and the small bowel. Hormones shown in animals to be tropic include enteroglucagon, neurotensin, epidermal growth factor, insulin-like growth factor-1 (IGF-1), glucagon-like peptide-2 (GLP-2), and gastrin. High levels of peptide YY have a role in slowing gastric emptying rate and enhancing the colonic brake phenomenon. Ghrelin, a recently identified hormone, has been investigated for potential satiety effects. Peptides such as peptide YY and enteroglucagon also slow intestinal motility. Transforming growth factor-β has been identified as having an inhibitory effect on bowel adaptation after loss of absorptive surface area.

## STAGES OF THERAPY

Initially, fluid and electrolyte replacement in the early postoperative period comprises the major focus of treatment. Replacement of nutrient losses and treatment of diarrhea quickly become additional challenges.

### Parenteral Nutrition

The practice of parenteral nutrition has become quite refined, involving development of age-related and disease-specific amino acid solutions and the recognition that there are age-dependent micronutrient requirements. The immediate postoperative period requires aggressive monitoring of fluid and electrolytes. A logical approach is to provide a standard parenteral nutrition solution, dependent on age of the patient, in combination with a more patient-specific fluid replacement protocol. Replacement fluids can be prescribed by monitoring electrolyte losses and overall volume loss in the previous 2–4 hours. Replacement of electrolytes lost in intestinal fluids may require very large quantities of electrolytes. Utilizing such protocols for replacement fluids rather than frequent altering of expensive total parenteral nutrition (TPN) solutions can be done quickly and easily at the bedside. Continued replacement of electrolyte and fluid losses can be difficult in the home environment; therefore, this constitutes one of the exclusions for home therapy.

TABLE II Average Caloric Requirements by Age Group

| Age | Kilocalories[a] |
|---|---|
| Premature infants | 120–150 |
| Newborns | 100–120 |
| 1–12 months | 100 |
| 1–6 years | 75–90 |
| 7–12 years | 60–75 |
| 13–18 years | 30–60 |
| Adult | 25–35 |

[a] Per kilogram body weight per day.

Initially, total parenteral nutrition solution should replace all basic nutritional needs. Table II identifies the average caloric requirements (kilocalories/kilogram/day) for different age groups. Table III lists the components of a standard pediatric total parenteral nutrition solution. Additional parenteral energy supply may be necessary during the early postoperative period or during times of stress, such as that related to fever or severe infections. One to two times the basal energy requirements may be required. Careful monitoring of parenteral nutrition via both clinical and laboratory parameters is required.

### Enteral Nutrition

When fluid and electrolyte status has been stabilized with the parenteral regimen, enteral feeding can be considered and should begin as soon as possible. In infants, elemental diets are delivered via continuous enteral infusion. Elemental formulas are well tolerated and avoid the risk of allergy to proteins in more complex feedings. Enteral feeding is typically started very slowly with a dilute concentration (5 cal/ounce), which is slowly increased to 20 cal/ounce for patients less than 1 year of age and 30 cal/ounce for older patients. When final concentration is reached, the volume is slowly advanced. The technique of reaching final concentration prior to increasing volume avoids fluid overloading for the patient also receiving parenteral nutrition.

TABLE III Standard Pediatric Total Parenteral Solution

| |
|---|
| Dextrose, 20% |
| Amino acids, 2.5% |
| Sodium chloride, 15 mEq/liter |
| Sodium acetate, 15 mEq/liter |
| Potassium phosphate, 20 mEq/liter |
| Calcium gluconate, 10 mEq/liter |
| Magnesium sulfate, 5 mEq/liter |
| Pediatric trace elements |
| Pediatric multivitamins |

The continuous and aggressive use of enteral nutrition should be encouraged unless significant dehydrating diarrhea ensues, in which case the infusion should be adjusted so that overall fluid balance improves. Continuous enteral infusion is inconvenient and is thought to decrease the normal developmental processes of eating. However, this can be managed later. Newer, small enteral infusion pumps along with backpack devices have been developed to allow the patient greater mobility. When long-term enteral nutrition is anticipated, i.e., greater than 3 months, gastrostomy tube placement facilitates continuous enteral feeding. The presence of a gastrostomy or nasogastric tube does not contraindicate feeding. However, continuous feeding does alter hunger mechanisms, and rejection of oral feeds is common. Use of continuous enteral feeding does decrease the likelihood of gastroesophageal reflux.

As the child advances in age, a more complex formula, such as a protein hydrolysate, is usually well tolerated. For patients older than 1–2 years of age, whole protein formulas stimulate further adaptation by increasing the workload of the surface epithelium. Carbohydrates in enteral formulas are present in the form of one or more sources, including extensively hydrolyzed starch and disaccharidases such as sucrose. Medium-chain fats, although well absorbed, are not as beneficial as long-chain fats in enhancing adaptation. Therefore, a mixture of both types of fat in the formula is most beneficial. Carbohydrate type is probably the least important type of required nutrient for patients with short bowel syndrome. However, lactose may be more slowly hydrolyzed than glucose polymers. Table IV lists some commonly used formulas for infants and children with short bowel syndrome. Theoretically, a formula with enhanced proportions of fat, even to 50% of the total daily energy intake, may be beneficial not only for delivering more calories in less volume, but also because high-fat formulas may slow gastrointestinal motility to enhance absorption.

Tolerance of continuous enteral infusion is based in part on stool losses; losses of greater than 40–50 ml/kg/day, especially if accompanied by the presence of positive reducing substances, suggest that enteral feedings should be reduced or halted. Infants should be given small volumes of nipple feedings to facilitate developmentally normal stages of eating. At the appropriate ages, introduction of solid foods should also be attempted. Caution should be given to types of solids initially utilized. Avoidance of foods containing high carbohydrate levels reduces osmotic losses. Meats are often well tolerated. Nutrient delivery by the oral route may not be significant due to malabsorption but is key in later stages of therapy. In older infants and toddlers, when the colon is intact, complex diets may be beneficial in enhancing colonic salvage of short-chain fatty acids.

TABLE IV Commonly Used Formulas

| Elemental | Semielemental | Whole protein |
|---|---|---|
| Neocate | Alimentum | Peptamen |
| Peptide 1+ | Pregestimil | Pediasure |
| Pediatric Vivonex | Nutramigen | Vital |
| Elecare | | |

## Chronic Therapy

Parenteral nutrition is weaned as enteral nutrition is advanced on a calorie-for-calorie basis. While continuous enteral nutrition is utilized, parenteral nutrition is suspended for a few hours each day, with the time off parenteral nutrition gradually increasing, decreasing total parenteral nutrition volume and calories. Eventually, delivery of TPN on an every-other-day basis is possible. This is most easily accomplished by continuous enteral delivery until parenteral nutrition is significantly reduced and the child remains stable. At that time, weaning of enteral nutrition can slowly be attempted as solid food intake increases. As the child ages, monitoring of weight gain becomes vitally important. Because caloric requirements do decrease slightly with advancing age, and if adequate intestinal adaptation occurs, many children whose weight seems to plateau over time can still be weaned successfully from parenteral nutrition.

Once parenteral nutrition is weaned, frequent monitoring of weight, height, and macro- and micronutrient intake becomes increasingly important. Deficiency states are incurred based on the area of intestine resected. It is not uncommon for children to require replacement of vitamin $B_{12}$, magnesium, and fat-soluble vitamins. If enteral nutrition advancement appears to stall, complications such as small bowel bacterial overgrowth or micronutrient deficiency should be considered.

## Complications

The most challenging complication of nutritional therapy in short bowel syndrome is diarrhea. Management should be based on etiology. Average stool losses should be established for each patient and alterations from baseline should be investigated. Possible changes in dietary intake and bacterial overgrowth are the most common causes of new-onset diarrhea. Utilization of bolus rather than continuous enteral feeding may result in an increased osmotic load and may not be well

tolerated. As the child grows, small, frequent meals, for example, may be more beneficial than three daily standard meals. In cases of bile acid malabsorption causing diarrhea, use of cholestyramine may be beneficial. However, it should be used with caution as the attendant sequestration of luminal bile salts may exacerbate fat and fat-soluble vitamin malabsorption. Antisecretory drugs are sometimes utilized. Somatostatin has been used to reduce diarrhea with modest efficacy short term, but long-term administration has not proved to be of benefit. Newer drugs such as racecadotril are currently under investigation. Antimotility drugs such as Imodium are often prescribed for patients with short small bowel and may be of benefit particularly if the ileocecal sphincter is intact. Antimotility drugs should be used with caution in children because they may enhance problems with small bowel bacterial overgrowth.

One of the most difficult complications to deal with in the therapy of short bowel syndrome is small bowel bacterial overgrowth. This condition occurs in virtually all patients; however, it does not become problematic in all. Diagnosis is difficult and no gold standard exists. Culture of jejunal aspirates, measurement of excess hydrogen production after a glucose load, serum D-lactate, and urine indican levels have all been attempted as possible correlates to pathological bacterial overgrowth. Symptoms include an increase in diarrhea, abdominal distension, and flatulence. At times, even bloody diarrhea may occur. Bacteria normally present the bowel have a role in deconjugating bile salts and produce micronutrients such as $B_{12}$. However, if bacterial numbers become excessive ($> 10^5$ jejunal and $> 10^8$ ileal), mucosal inflammation may result. Another significant complication of small bowel bacterial overgrowth is D-lactic acidosis. Particularly in infants and small children, this can lead to lethargy and even coma.

Empiric treatment of small bowel bacterial overgrowth with antibiotics is often helpful in establishing the diagnosis. Broad-spectrum antibiotics such as oral gentamicin, trimethoprim sulfate, and/or metronidazole are often utilized initially. Low doses may result in significant improvement in symptoms. Endoscopy is rarely helpful, except in evaluating the presence of enteritis and colitis. If present, these situations may also respond to antiinflammatory therapy with mesalamine or even corticosteroids. If beneficial, antibiotic therapy is often not required continuously, but may be used on a rotating schedule. Eventually, the development of resistant organisms may require the alteration of antibiotic type. Use of probiotics may also be beneficial in preventing or modulating the response of more harmful or excessive bacterial species.

TABLE V Commonly Acquired Nutrient Deficiencies

| Nutrient | Signs and symptoms |
|---|---|
| Vitamin A | Night blindness |
| Vitamin D | Bony demineralization |
| Vitamin $B_{12}$ | Megaloblastic anemia |
| Magnesium | Lethargy and tetany |

As food-based intake is advanced, specific nutrient deficiency states may occur when supplemental enteral formula is no longer required. Table V lists commonly acquired nutrient deficiencies. Nutrient supplements are readily available and usually dosing can be adjusted based on blood levels of the nutrients. Magnesium presents a particular challenge because supplementation with almost any magnesium supplement can enhance diarrhea. Careful administration and followup monitoring of supplements are required, especially when levels become critically low. The development of acid peptic disease commonly occurs in children with short bowel syndrome. Many pediatric patients with short bowel syndrome eventually become symptomatic with acid reflux and require neutralizing or acid suppression medications on a long-term basis.

The most life-threatening complication of long-term nutritional therapy in infants with short bowel syndrome is parenteral nutrition-related liver disease. The etiology of this entity is not well understood. Toxicity of amino acid solutions, excess administration of lipid solutions, production of toxins by bacteria in the bowel, excessive nutrient administration, toxicity of unknown substances in the parenteral nutrition solution, and absence of stimulation of gastrointestinal hormones have all been implicated as possible contributing factors. It is well understood that even minimal enteral nutrition is important in lessening the impact of this complication. Ursodeoxycholic acid has been advocated to prevent the development of parenteral nutrition liver disease. Recurrent central venous catheter sepsis has been more recently identified as a possible factor in the development of TPN-associated liver disease. Efforts should be made to prevent as many of these complications as possible. In extreme cases of intestinal failure with mild TPN-associated liver disease, reversal of liver disease has been noted following successful intestinal transplantation.

## SURGICAL THERAPY AND TRANSPLANTATION

Patients with short bowel syndrome who have undergone intestinal resection frequently experience

problems with anastomotic strictures and ulcerations. These can occur at any time, but typically do so within a few years after the initial resection. Symptoms include recurrent or sudden anemia, blood in the stools, or progressive worsening of vomiting and abdominal bloating. The adaptive response, although beneficial in enhancing the absorptive surface area, may be become extreme and result in dilatation of the bowel, with poor motility and significant small bowel bacterial overgrowth. Such bowel dilatation can be identified on radiographic imaging studies and may be amenable to surgical tapering with or without concomitant bowel lengthening (Bianchi procedure). These procedures, if done at centers with expertise in performing them, may be beneficial in alleviating symptoms without sacrificing intestinal absorptive surface area. Surgical procedures designed to slow intestinal transit via creation of intestinal valvelike areas or reversed intestinal segments are not recommended. Fundoplication is sometimes necessary in patients who experience significantly altered upper gastrointestinal motility.

Intestinal or combined liver/intestinal transplantation has become an alternative, although not an early interventional strategy, for patients requiring chronic parenteral nutritional support due to short bowel syndrome. Transplantation prior to irreversible liver or bowel failure is often met with great success. At the present time, it is not possible to predict which patients will fail intestinal rehabilitation. Attempts to predict ultimate failure of parenteral nutrition have centered on criteria including the presence of less than 30 cm of small bowel, absence of the ileocecal valve, some colon resection, only minimal tolerance of feedings 2 months after resection, patients without a jejunum or ileum, patients with poor quality of residual bowel, and patients with repeated sepsis episodes. Advances in surgical technique and immunosuppression have enhanced survival; however, graft rejection and complications of immunosuppression may ultimately occur because these patients survive longer. New medications for immunosuppression, such as interleukin-2 antagonist, bone marrow augmentation, and tolerance induction, have all enhanced the success of intestinal transplantation. Results vary significantly among centers performing intestinal transplants, with an overall 1- to 2-year survival at 75% decreasing to about 50% at 3–5 years. The shortage of donors remains a significant problem. Although intestinal rehabilitation may offer the best chance for a meaningful quality of life and the best chance for longevity, transplantation as a newer form of therapy may be an option for patients failing on parenteral nutrition.

## PROGNOSIS

Parenteral and enteral nutrition programs remain the mainstay of therapy for infants and children with short bowel syndrome. The majority of these patients, if adequately managed, will require parenteral nutrition only as an interim phase of rehabilitation. Some patients will eventually develop life-threatening complications, including liver disease. Transplantation of either the bowel or the bowel and liver have become possible options for selected patients unable to succeed with parenteral nutrition. Although home-based parenteral nutrition does permit optimal psychosocial development, it requires the utilization of an aggressive nutrition team approach by nurses, physicians, and nutritionists. Augmentative surgical procedures are sometimes helpful in restoring bowel function.

### See Also the Following Articles

**Bacterial Overgrowth • Enteral Nutrition • Parenteral Nutrition • Transplantation Immunology**

### Further Reading

Andorsky, D. J., Lund, D. P., Lillehei, C. W., *et al.* (2001). Nutritional and other postoperative management of neonates with short bowel syndrome correlates with clinical outcomes. *J. Pediatr.* 139(1), 27–33.

Georgeson, K., Halpin, D., Figueroa, R., *et al.* (1994). Sequential intestinal lengthening procedure for refractory short bowel syndrome. *J. Pediatr. Surg.* 29(2), 316–320.

Hart, M. H. (1992). Growth factors in intestinal resection. *J. Pediatr. Gastroenterol. Nutr.* 14, 2.

Jeppson, P. B., Hartmann, B., Thulesen, J., *et al.* (2001). Glucagon-like peptide 2 improves nutrient absorption and nutritional status in short bowel patients with no colon. *Gastroenterology* 120(4), 806–815.

Kaufmann, S. S., Atkinson, J. B., Bianchi, A., *et al.* (2001). Indications for pediatric intestinal transplantation: A position paper of the American Society of Transplantation. *Pediatr. Transplant.* 5(2), 80–87.

Michail, S., and Vanderhoof, J. A. (1996). Parenteral nutrition in clinical practice. *Ann. Nestle* 54, 53–60.

Nightingale, J. M., Kamm, M. A., van-der-Sijp, J. R., *et al.* (1993). Disturbed gastric emptying in the short bowel syndrome. Evidence for a "colonic brake." *Gut* 34(9), 1171–1176.

Nightingale, J. M. D., Kamm, M. A., van der-Sijp, J. R. M., Ghatei, M. A., Bloom, S. R., and Lennard-Jones, J. E. (1996). Gastrointestinal hormones in short bowel syndrome. Peptide YY may be the "colonic brake" to gastric emptying. *Gut* 39, 267–272.

Nucci, A. M., Barksdale, E. M. Jr., Beserock, N., *et al.* (2002). Long-term nutritional outcome after pediatric intestinal transplantation. *J. Pediatr. Surg.* 37(3), 460–463.

Vanderhoof, J. A. (1996). Short bowel syndrome. *In* "Pediatric Gastrointestinal Disease" (W. A. Walker, P. R. Durie, J. R. Hamilton, J. A. Walker-Smith, and J. B. Watkins, eds.), 2nd Ed., pp. 830–840. Mosby, St. Louis, Missouri.

Vanderhoof, J. A. (1999). Short bowel syndrome: Parenteral nutrition versus intestinal transplantation. *Pediatr. Nutr. ISPEN* 1(1), 8–15.
Vanderhoof, J. A., Young, R. J., Murray, N., and Kaufman, S. S. (1998). Treatment strategies for small bowel bacterial overgrowth in short bowel syndrome. *J. Pediatr. Gastroenterol. Nutr.* 27, 155–160.
Vargas, J. H., Ament, M. E., and Berquist, W. E. (1987). Long term home parenteral nutrition in pediatrics: 10 years of experience in 102 patients. *J. Pediatr. Gastroenterol. Nutr.* 6(1), 24–32.
Warner, B. W., Vanderhoof, J. A., and Reyes, J. D. (2000). What's new in the management of short gut syndrome in children. *J. Am. Coll. Surg.* 190(6), 725–736.

# Sigmoidoscopy

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**cathartic** An agent that results in the purging of bowel contents.
**colitis** Inflammation of the colonic mucosa; may be acute or chronic.
**fissure** A painful split in the mucous membrane of the anus.
**hemorrhoids** Varicosities of the external hemorrhoidal veins that may result in a painful swelling at the anus and have a propensity for bleeding.
**mini-perforation** A small rent in the bowel, which typically is contained by the overlying omentum and heals without the need for surgical repair.
**perineum** The external region between the anus and the genitalia.
**pneumatosis coli** The presence of gas-filled cysts within the intestinal mucosa, which may occur after colonic insufflation or with colonic ischemia.
**postpolypectomy syndrome** An acute syndrome composed of pain, fever, and focal colitis stemming from transmural thermal injury following the removal of a polyp with cauterization.
**proctitis** Inflammation of the rectal mucosa; may be acute or chronic.
**sigmoidoscopy** A technique for obtaining intralumenal visualization of the rectum, sigmoid, and, usually, left colon, utilizing a fiber-optic endoscope.
**splenic flexure** The section of colon representing the transition from the transverse colon to the left colon, typically located in the left upper quadrant of the abdomen, inferior to the spleen.
**tenesmus** A painful cramping sensation of incomplete defecation, accompanied by ineffectual straining to further evacuate the bowel.
**valves of Houston** The three or four crescentic transverse folds of the rectum.

**Sigmoidoscopy, by definition, is a manual technique whereby intralumenal visualization of the rectum and sigmoid colon is accomplished using a fiber-optic endoscope. However, the procedure generally includes examination of the left colon as well. With the advent of flexible endoscopy in the 1960s, it became possible to survey the entire large intestine. Yet, even as full colonoscopy has become an important tool in the workup and surveillance of various conditions, flexible sigmoidoscopy continues to play an important role in gastrointestinal diagnostics. That role is based on several key facts: (1) flexible sigmoidoscopy is safe and, most often, does not require sedation; (2) the procedure can be performed relatively quickly, in an office setting, and by a variety of appropriately trained health care providers; and (3) findings in the distal colon often answer important clinical questions regarding disease states such as acute colitis, chronic colitis, and rectal bleeding. Although evaluation of the sigmoid colon can also be accomplished with a rigid sigmoidoscope, this technique has largely been supplanted by flexible sigmoidoscopy, which is better tolerated by patients and typically allows for a more extensive examination. Therefore, the focus of this article will be on the use of flexible sigmoidoscopy.**

## PATIENT PREPARATION

Preparation for sigmoidoscopy is far easier for the patient than that necessary for colonoscopy. As only the distal portion of the colon needs proper cleansing, enemas prior to procedure often suffice. A common

prescription is one or two hypertonic phosphate enemas taken an hour prior to examination. Delay of over an hour from the last enema may allow more proximal fecal debris to migrate to the left colon. Many different bowel preparations for sigmoidoscopy have been studied and recommendations vary. Some investigators advocate using oral cathartics, such as magnesium citrate, the night before the examination, followed by two hypertonic phosphate enemas on the day of the exam. Others suggest using oral laxatives, such as magnesium citrate or oral hypertonic phosphate solution, alone or in combination with a stimulant laxative, such as bisacodyl. Although hypertonic phosphate enema is the standard regimen, alternative preparations can be used based on the preferences of the examiner and medical history of the patient. Adding oral cathartics the night before a procedure will usually lead to a better preparation and might be useful in the patient in whom enemas alone are suspected to give marginal results. Such a patient might be someone with severe diverticular disease, one with poor anal sphincter tone, who has difficulty retaining an enema, or someone with a poor preparation previously. However, patient tolerance and satisfaction may be compromised, in light of the common side effects of oral laxatives, such as abdominal cramping, nausea, and vomiting. The goal of the bowel preparation is threefold: safety, efficacy, and tolerance. A properly cleansed bowel allows the endoscopist to advance the instrument with a clear view of the lumen and hence, achieve a thorough and safe examination. A poor preparation with residual stool may result in an inadequate assessment of the colonic mucosa, as well as an increased risk of perforation due to suboptimal visualization of the colonic lumen. Pathology may be missed with stool in the way, even with honest efforts to irrigate and aspirate. Therefore, the patient is best served by having the examination rescheduled. Finally, a good colonic preparation usually yields a shorter, more comfortable examination for the patient. Minimizing discomfort is paramount for ensuring compliance with potential future examinations.

When choosing a preparation, it is important to account for the medical condition of the patient. Oral hypertonic sodium phosphate solutions are generally contraindicated in patients with renal impairment, due to the potential for clinically significant hyperphosphatemia and/or hypocalcemia. Similarly, patients with renal impairment should avoid magnesium citrate preparations, due to the risk of developing hypermagnesemia. Sodium phosphate solutions may also be hazardous in those with congestive heart failure or cirrhosis, due to the large sodium load that occurs with these preparations. Other conditions that may carry an increased risk for sodium phosphate-induced hyperphosphatemia include severe ulcerative colitis and pregnancy (the placenta actively transports phosphates). Phosphate preparations can also cause epithelial sloughing and/or aphthous ulcerations, which may cause confusion in cases of suspected colitis. Mucosal biopsies will usually distinguish preparation-induced changes from a chronic, idiopathic colitis. In moderate to severe colitis, with significant diarrhea, bowel preparation may not be needed at all, as any retained stool will be liquid and easily aspirated. Alternatively, tap water enemas may be used.

Some patients with anorectal disease, particularly those with fissures, or patients with low thresholds for discomfort may need topical anesthetics, such as viscous lidocaine, or even conscious sedation for the examination. If conscious sedation is anticipated, then overnight fasting is necessary to reduce the chance of nausea, vomiting, and pulmonary aspiration. In this circumstance, cardiopulmonary monitoring is also required, as well as the presence of providers that are trained and certified in the administration of conscious sedation.

## SETTING UP

It is common for patients to experience varying degrees of anxiety prior to the procedure. Therefore, the procedure should be reviewed in detail. The patient should be reminded of why the test is being performed, abnormal findings that might reasonably be anticipated, and the fact that mild discomfort may be experienced. The patient should know that discomfort can be ameliorated by removing air or partially withdrawing the scope, to avoid the notion that minor discomfort should necessarily lead to aborting the procedure. Risks ought to be recounted, including discomfort, bleeding (especially if biopsies are taken), and perforation. In the patient receiving conscious sedation for the test, the potential for adverse reaction to a sedative must be discussed and a review of comorbid conditions, medications, and allergies is necessary. It is important to provide ample time for patients to have any questions answered and for informed written consent to be obtained from the patient or designated surrogate.

Once the patient is ready, he or she should lie on the examination table with the left side down and facing away from the examiner. Most endoscopists will use video endoscopes, as opposed to fiber-optic scopes that utilize an eyepiece. The endoscopic power/light source will be alongside the endoscopist to the right, toward the patient's feet, with the video monitor on the

other side of the table, facing the patient and the endoscopist. If a nurse is assisting the procedure, he or she should stand at the patient's feet, on the other side of the light source, so as to most easily hand endoscope accessories to the endoscopist. The light source should be turned on and checked to ensure that air insufflation, suction, and lens-washing functions all operate properly. Discovering technical malfunctions during the procedure can compromise thorough examination as well as patient confidence. At the ready, the endoscopist should have lubricating jelly, a washcloth or gauze for use if needed in handling a lubricated instrument, and a water basin with a prefilled 60 cc syringe for irrigating stool through the endoscope channel.

Next, visual inspection and a digital rectal exam are performed. Rectal examination allows the examiner to lubricate the anal canal (a generous amount of jelly is advised) and to palpate the anal canal and lower rectum. This step is critical for finding pathology of the perineum and anal canal. Conditions such as external hemorrhoids and anal fissures may be best appreciated at this time. The patient should be informed that the maneuver is to occur and it should be performed slowly. Unexpectedly cold lubricant, rapid insertion, or a rough examination may heighten anxiety and possibly lower the threshold for perceived discomfort during the endoscopy. A tender fissure or inflamed hemorrhoids may warrant the use of anesthetic jelly during examination. Circumferential palpation of the canal and lower rectum is important, as this area is the most difficult to examine endoscopically, even with retroflexing the scope. Furthermore, on occasion, lesions that are not easily distinguished visually, such as squamous cell cancers of the anal canal or submucosal lesions, might be palpated.

## THE SIGMOIDOSCOPE

Most commonly, flexible sigmoidoscopy is performed with a 60 cm endoscope with a 12 mm outer diameter. All standard endoscopes are right-handed, so that the shaft is grasped with the right hand and the control head with the left. Within the shaft, either fiber-optic bundles (in the older models) or an electronic chip carries the visual image either to a focusing lens beneath an eyepiece or to a video processor, respectively. The shaft also carries the cables that allow the directional dials to control the scope tip, as well as an open channel through which instruments can be passed (forceps, snare, cautery probe, injection needle, etc.). At the control head are two main buttons, two dials, and an entry port for the internal channel. The upper button is depressed for suction, with the degree of depression corresponding to the suction pressure. The lower button has a central hole, which is covered to activate air insufflation at the endoscope tip. Tapping at the button allows for fine control of delivered air volume. Depressing the lower button fully causes the water irrigation system to clean the lens at the scope tip by washing across it. Some endoscopes have other buttons for freezing or capturing images to the video processor. The inner dial controls up and down tip deflection and the smaller outer dial controls left and right tip deflection. On most flexible sigmoidoscopes, the tip can deflect 180° in the up or down direction and 160° left or right. Brakes are usually mounted on these dials to lock them if one wishes to maintain a given tip deflection or neutral position. An umbilical cord inserts into the control head and connects it to the power source that controls the light, air, and irrigation systems. The scope head should be held in the left hand so that the thumb can reach both directional dials and the forefinger comes around to the front of the head to manage the buttons.

Occasionally, the standard flexible sigmoidoscope shaft may be too stiff for some patients. The advantage of a relatively stiff-shafted instrument in the colon is that it reduces scope looping in the often-windy left colon. However, when the sigmoid colon is more tortuous or has restricted mobility, owing to previous surgeries or inflammatory (e.g., diverticular) processes, a standard sigmoidoscope may cause painful looping, as it stretches the bowel upon its mesentery. In such cases, a thinner, more flexible instrument may be helpful. For these occasions, a standard gastroscope is thinner (0.96 cm) and longer and has greater tip deflection. Such an instrument can more easily negotiate sharper turns in a tortuous colon with less pressure applied and should allow the endoscopist to reach the splenic flexure with less patient discomfort.

## SIGMOIDOSCOPIC TECHNIQUE

In general, the sigmoidoscope should be advanced until the splenic flexure is reached, solid stool is encountered, or the patient experiences appreciable discomfort. Thus, a proper exam requires some skill on the part of the endoscopist, in order to reach the flexure without running out of scope or convincing the patient never to return. A complete exam usually takes 5 to 10 min.

After the rectal examination, the patient should be told that the endoscopy is to begin and additional lubricant is applied to the distal portion of the endoscope tip. The scope is then inserted. Usually the scope will meet mild resistance at the anal sphincter muscles and then slip through the anal canal. Placement of the right forefinger on the tip of the scope might help guide it into the anal canal.

Once the scope has entered the rectum, it should be withdrawn a few centimeters, air should be insufflated into the rectum, and the tip should be deflected upward a bit. If not pulled back, the scope will likely be pressed against the anterior wall of the rectum with a pink image on the monitor. After the rectum is partially inflated and the lumen is visible, the endoscope may be advanced, with "dark" areas signifying the lumen ahead. In advancing the scope, most endoscopists prefer to guide the instrument with use of the up/down dials and right-handed torque of the shaft. Left and right tip deflection is rarely a prominent feature of scope advancement through the colon, as it is usually simpler to "feel" the turns by gently rolling the scope between the right thumb and forefinger (with or without the middle finger).

Forward progress and risk reduction require that the lumen be visualized at all times. This is not always easy as the bowel has continuous underlying peristalsis and some turns may be sharp. Yet, the most important rule of intestinal endoscopy is to always pull back when the lumen is not clearly visible. Likewise, if blanching of blood vessels is observed, excessive pressure is being exerted on the mucosa and the scope should be promptly withdrawn until a view of the lumen is restored. One should never worry about losing ground in falling back past a turn. Sometimes, sharp turns require pulling back, deciding which angle to take, and then proceeding anew. Once a turn is made with the scope tip, pulling the shaft back slightly, with the scope tip still deflected, usually allows for the lumen to come back into view. Care must always be taken to advance the scope only when the path of the lumen is certain. "Blind pushing" may lead to traumatic complications and must be avoided. Greatest care must accompany the examination of the colon with dense diverticular disease. Large, thin-walled diverticula may mimic the lumen and thus every maneuver with the scope tip must be slow and cautious. When a sharp turn is present and the direction is known, the endoscopist is often tempted to "slide by," that is, gently try to advance the directed scope tip, hoping the lumen will soon come into view. Slide-by maneuvers do carry some risk and should generally be avoided. Sometimes it can be avoided by either hooking a turn and pulling back on the scope shaft, thus bringing the lumen into view, or by pulling back, desufflating the segment of bowel, which may decrease the acuity of the angulation, and slowly advancing through a "memorized" trail with only a small amount of dark lumen leading the way. The circular muscles in the wall of the colon are helpful, as the lumen will follow in the direction of the concave contours, which usually are readily apparent through the mucosa.

Inevitably, when pushing an endoscope into the colon, loops will occur. In looping, forward pressure on the back end of the scope forces the shaft into the wall of the bowel behind the scope tip. The only way for looping not to happen is for the bowel to resemble a straight pipe, which, unfortunately, does not commonly occur. In other words, looping always occurs and forward progress requires that the loop be "reduced." A loop can be removed by pulling back on the scope and usually by trying to torque the scope in the direction opposite to the dominant twist of the bowel, a maneuver that often calls upon trial and error. Loops in the sigmoid colon are most often "alpha" loops, which are usually reduced by torquing the shaft clockwise and pulling the scope backward. Remember that with every turn made by the scope tip, some looping becomes inherent in the shaft. For this reason, the endoscopist should try to withdraw somewhat after every turn. In doing so, the bowel can be straightened along the shaft of the scope, allowing for further forward progress. In unsedated sigmoidoscopy, no significant looping will escape the endoscopist's consciousness, as the patient will become uncomfortable when the bowel is stretched on its mesentery. Passing the scope more proximally will, usually, occur only after reducing the loop and restoring the patient's comfort. In the patient with known or suspected acute colitis, looping should be avoided at all costs, as the less sturdy bowel wall may more easily succumb to traumatic wall pressures applied by the scope.

As mentioned previously, the anatomic goal of sigmoidoscopy is to reach the splenic flexure, the proximal end of the "left colon." Although there are no consistent landmarks in the large intestine between the anal canal and the appendix and ileocecal valve, there are a few ways to help decide where the scope tip might be. One endoscopic marker to look for is the spleen itself. The spleen and liver both are clearly seen through the thin-walled bowel. Unfortunately, a splenic or hepatic impression sometimes occurs in more than one segment of colon. Light pressure on the anterior aspect of the abdominal skin may yield a gross idea of where the scope tip is in the abdomen, although knowing that the tip is somewhere in the left upper quadrant or mid abdomen is not too helpful. The most helpful markers are the appearance of the bowel and the centimeter markings on the shaft of the scope. (Note that the depth of scope insertion has informational value only if the endoscope is fully reduced, as looping will always give the misimpression of the tip being more proximal in the bowel.) When the scope is straight, the splenic flexure is usually approximately 40–45 cm from the anus. Nevertheless, twice that length of scope can easily be pushed

into the bowel before reaching the splenic flexure, if looping is allowed. Of course the standard sigmoidoscope is only 60 cm, meaning that loops must be reduced systematically.

The appearance of the bowel may also be useful. The capacious rectum is approximately 10–15 cm long and is partially divided proximally by the valves of Houston, which causes the entering endoscope to slalom a bit before reaching the rectosigmoid junction, at which time the lumenal diameter narrows appreciably. The sigmoid colon runs approximately 15–20 cm, but is typically quite serpiginous and its length varies widely among patients. The junction of the sigmoid and descending colons is usually not evident endoscopically, as it is on barium enema. One may hit a long "straight-away," which usually means that the scope tip is in the descending colon and that the next major turn will be the splenic flexure. Yet, some patients may have a relatively short descending colon or one that is as tortuous as the sigmoid due to diverticular or other inflammatory disease, previous surgery, or laxity in the mesentery, which may come with age. The transverse colon usually has a typical triangular shape to the colonic haustra and a relatively straight course. Seeing these identifying marks allows the endoscopist to comfortably presume that the splenic flexure has been traversed.

In truth, the splenic flexure is not reached as commonly as it should be during sigmoidoscopies. One study using magnetic imaging to determine scope tip location discovered that a quarter of examinations failed to reach the sigmoid-descending junction and fewer than 10% reached the splenic flexure. The same study used colonoscopes to demonstrate that, on average, 75 cm of scope was needed to reach the splenic flexure. Such information confirms the importance of always trying to continually remove loops, especially when using a 60 cm scope. Keeping the endoscope straight and reproducibly reaching at least the descending colon, however, takes practice and skill. In that vein, effective sigmoidoscopy (particularly for screening purposes, where depth of insertion may determine findings) requires experience and continued repetition.

Once the splenic flexure is reached, solid stool is found, or the patient is overly uncomfortable, the process of withdrawing the scope begins. It is during withdrawal that more careful endoscopic evaluation of the bowel occurs. During insertion it is generally wise to avoid full insufflation, which makes the bowel longer, the turns sharper, and the patient more distended. Yet, on withdrawing the scope, care should be taken to see the entire mucosal surface, which necessitates some insufflation. Much of this air can be suctioned back out as the examination progresses distally. Many endoscopists reserve mucosal biopsies or polypectomies for the withdrawal stage of the test. (A caveat to this option is that polyps that are small or in awkward spots, such as behind folds, should be removed on insertion lest they not be found on withdrawal.) Withdrawing is technically easier, as turns can be more readily anticipated and scope loops, and hopefully air, are being removed, allowing the patient more comfort. Here, it is important to keep the lumen centered in view with fine tip control. Some advocate locking the right/left dial to minimize unwanted minor tip deflections and using gentle torque and the up/down dial to maintain proper bowel visualization. Gentle torquing of the shaft allows the endoscope tip to swivel a bit, enhancing visualization behind folds. If the scope slips back too quickly and a segment of colon is not adequately inspected, the endoscopist should advance once again, so as to avoid missing any pathology. Similarly, if the patient passes flatus, which should not be discouraged as it promotes comfort, or bowel spasm occurs, the endoscopist should stop and re-inflate the segment. Liquid stool should be suctioned out and mucosa with adherent stool should be irrigated with water. These cleaning chores are best avoided during scope insertion, unless the lumen cannot be adequately seen, as they lead to excessive air insufflation early on, making the rest of the insertion process more difficult.

After the scope has been pulled back into the rectum and the rectum examined, retroflexion is performed. The tip should be right at the anal verge and all dial brakes should be released so the scope is as flexible as possible. The scope is then slowly advanced as maximal upward tip deflection is applied with concomitant torque in either direction. This maneuver allows the tip to face back toward the anus and the scope shaft itself. Here, internal hemorrhoids are best seen, as is the most distal rectum. Without retroflexion, many low rectal lesions will be missed. Retroflexion can be uncomfortable for the patient, so the patient should be warned of impending rectal pressure, which will signify the end of the procedure.

Although the variety of endoscopic findings is beyond the scope of this article, several findings bear mention. Polyps appear as raised mucosal lesions; most are only slightly raised off the surface, but some may be large and rounded on stalks. Tiny polyps may be removed (usually with biopsy forceps) during the exam to determine whether they are adenomatous, and thus carrying malignant potential, or hyperplastic, without any malignant potential. Hyperplastic polyps generally are rather small, sessile, and smooth textured, whereas most adenomas have a slightly corrugated surface, although appearances may sometimes be misleading. If

larger (greater than 3–4 mm) or multiple polyps are found, concern for likely adenomas should lead to scheduling a colonoscopy, obviating sampling efforts. Similarly, if a tumor is found, colonoscopy will be necessary to "clear" the proximal colon prior to surgical evaluation. Diverticula, vascular malformations, hemorrhoids, or mucosal inflammation should always be noted, as they may explain previous or future bleeding episodes.

## INDICATIONS

### Average-Risk Cancer Screening

The most common application of flexible sigmoidoscopy is for colon cancer screening in the average-risk adult. Colon cancer is the second most common cause of cancer-related death in the United States. The survival rates for early-stage malignancies are excellent, but rather poor for advanced tumors. Furthermore, it is well established that adenomatous colon polyps are the precursors of adenocarcinomas of the colon and rectum. Therefore, screening people for early cancers and for polyps that may lead to cancers is worthwhile and has been shown to save lives. Screening modalities currently include fecal-occult blood testing, sigmoidoscopy, barium enema, and colonoscopy. Computerized tomographic (CT) colonography is another modality that is being investigated as a screening technique, but is currently considered experimental and has not yet been approved for this indication. Endoscopic screening is the most sensitive way to find neoplasms, and polyps greater than 5 mm in size are rarely missed. For average-risk patients, the American Cancer Society, American College of Gastroenterology, and the Gastrointestinal Consortium all recommend combining yearly three-sample fecal-occult blood tests with sigmoidoscopy every 5 years or performing colonoscopy every 10 years. The Preventive Services Task Force also recommends sigmoidoscopy every 5 years after the age of 50, with or without concomitant yearly fecal occult-blood testing. The obvious shortcoming of sigmoidoscopy is missing proximal lesions and between 20 and 50% of patients with polyps will have only proximal lesions. In fact, there has been a "rightward shift" in colorectal neoplasia, so that polyps and cancers are found in the proximal colon more commonly than a few decades ago. Yet, as there are insufficient resources to perform screening colonoscopies for the entire population, fecal occult-blood testing and sigmoidoscopy remain important tools to this end. In truth, the addition of fecal occult-blood testing to sigmoidoscopy only marginally increases the yield of advanced (10 mm of larger) neoplastic lesions, from 70 to 76%. Yet, fecal occult-blood testing is relatively inexpensive and will yield more colonoscopies, which means finding more cancers. (Note that patients with positive fecal occult-blood testing, known or suspected adenomatous polyps on sigmoidoscopy, family history of a first-degree relative with colon polyps or cancer, and patients otherwise at above-average risk for colorectal cancer should undergo colonoscopy and are not appropriate for "screening.")

### Adjunct to Barium Enema in Screening

Barium enema, although less sensitive than colonoscopy for polyps and cancers, is still used for average-risk screening and above-average-risk indications for colonic evaluation (such as positive fecal occult-blood testing, family history of neoplasia). When barium enema is performed, a catheter-tipped balloon is inserted into the rectum and thereafter barium is introduced to the colon in a retrograde fashion. The presence of the balloon prevents complete visualization of the rectum. Thus, whenever barium enema is used to survey the colon, flexible sigmoidoscopy (or at least proctoscopy) is necessary to complete the task.

### Workup of Minor Rectal Bleeding in Patients Less Than 40 Years of Age

The passage of red blood from the rectum generally results from sources in the rectum and anal/perianal regions. Hemorrhoids, anal fissures, proctitis, and rectal cancers are the most common explanations. Other precipitators may include distal neoplasms, proctitis, left-sided colitis, diverticula, angiodysplasias, or colonic ulcers. Some of these conditions may involve multiple segments of the colon, but the finding of a right-sided lesion as an explanation for small amounts of visible red blood, with a normal left colon, is unusual. Thus, when a patient describes seeing small amounts of blood with the stool, or just on the toilet tissue, examination of the distal 60 cm of the colon should be sufficient. However, several studies have shown that patients with nonemergent rectal bleeding may have above-average risk for colorectal cancers. Because of an increased risk for advanced neoplasia, if a patient is over 40 years of age and has not had a previous colonoscopy, a complete examination of the colon is indicated for the evaluation of rectal bleeding. In the patient under 40 years of age, without other risk factors for colorectal cancer, flexible sigmoidoscopy is the recommended test. Obviously, the specific clinical history should help guide management as well. For instance, the new onset of blood mixed with stool, unrelated to any straining, tenesmus, or other

symptoms common to anorectal pathology, should heighten concern for a neoplasm. In such a case, colonoscopy may be the most appropriate study. Additionally, a patient with benign findings on sigmoidoscopy who continues to bleed, despite directed conservative measures, deserves colonoscopy to rule out missed or right-sided lesions.

### Suspected Acute Colitis

In the patient complaining of recent cramping, altered bowel consistency, and/or bleeding per rectum, a diagnosis of acute colitis must be considered. Causes of acute colitis are varied and include infections, ischemia, mucosal toxicity related to medications, chemotherapy or radiation, flares of ulcerative colitis or Crohn's colitis, and diverticulitis. Usually the clinical scenario lends to likely etiologies. For instance, the hospitalized individual on antibiotics with new fever and diarrhea may have infectious colitis due to infection with *Clostridium difficile*, whereas an elderly person with vascular disease and new-onset cramping and bloody diarrhea likely suffers from ischemic colitis. Often, empiric therapy for acute colitides is reasonable. Yet if the diagnosis or cause is not certain, empiric therapy may be hazardous to the individual, or symptoms are severe or unresponsive to empiric therapy, further investigation is warranted. Flexible sigmoidoscopy, with or without biopsies, will generally suffice, as it is uncommon for an acute colitis to solely involve the proximal colon. In fact, bowel preparation is often not necessary, as these patients rarely have significant amounts of solid stool in the distal colon and the preparation may alter or worsen mucosal findings. Biopsies of the affected mucosa may be quite helpful, but, sometimes, endoscopic views will clinch a diagnosis, such as the typical pseudomembranes of *C. difficile*, the hypervascular markings of radiation proctitis, or the segmental distribution of ischemic colitis. On occasion, acute colitis may warrant full colonoscopy as in suspected Cytomegalovirus-related colitis, which may affect only the proximal colon, or when CT scanning shows a proximal colitis.

### Surveillance of Chronic, Left-Sided Disease

Ulcerative colitis, and less often Crohn's colitis, may be limited to the distal colon. In patients with pancolitis, increased risk of colorectal cancer has led to regular surveillance programs for patients with duration of disease over 8 years. In patients with distal ulcerative colitis only, the time to increased cancer risk is unclear, but most physicians start surveillance programs at 12 years from diagnosis. For these patients, surveillance biopsies of the involved bowel segments can be performed with sigmoidoscopy (although some alternate sigmoidoscopic surveillance of the affected bowel with full colonoscopic surveillance). Some patients with familial adenomatous polyposis will have undergone colectomy but have an ileocolonic anastomosis with a retained rectal remnant. These patients need continued surveillance of the rectum given the persistent risk of cancer involving the rectum.

### Directed Investigation of Suspected Left Colon Lesions

Not infrequently, colonoscopy or sigmoidoscopy is precipitated by abnormal radiographs. A patient at low risk for colorectal cancer (e.g., a person under 40 with no family history) or who is a poor candidate for colonoscopy (very elderly, postmyocardial infarction, critically ill, etc.) may have a suspicious finding on barium enema or CT scan that seems to involve the distal bowel. This finding may represent a mass, wall thickening, ulceration, suspected colonic invasion by tumor in an adjacent organ, or simply radiographic artifact. In such a scenario, an evaluation of the colon limited to the distal bowel may suffice. Similarly, in a patient with known gynecologic or urologic malignancy there may be suspicion of colonic involvement, based on hematochezia or suggestive radiographs. If colonic extension of tumor is suspected in the pelvis, as is commonly the case, sigmoidoscopy is adequate to answer the question.

### Directed Investigation or Treatment of Known Left Colon Lesions

Uncommonly, a distal colonic lesion needs treatment and the more proximal colon has already been cleared with colonoscopy. An endoscopist may wish to revisit a recent colonic polypectomy site, when residual adenomatous tissue is suspected. Another occasion is planned therapy for radiation proctitis with endoscopic fulguration or vaporization. Note that whenever electrical or photochemical therapies are used in the colon, even in unsedated patients with lesions well within the reach of the sigmoidoscope, a full bowel preparation is necessary. If the bacteria that produce hydrocarbon gases are not purged from the colon, the aforementioned energy sources could, theoretically, spark an explosion within the bowel lumen.

### Colonic Symptoms without Bleeding

The use of lower endoscopy in the evaluation of chronic abdominal pain, altered bowel habits, or weight

loss is of low yield, although commonplace. Colonic neoplasia will seldom explain constipation, but if present will occur on the left side where stool is more formed and subject to partial obstruction more easily. Low abdominal pain sometimes is explained by diverticular disease (relapsing diverticulitis) or, more commonly, by spastic colon, which often can be appreciated endoscopically. Colonic insufflation may often reproduce a patient's reported pain, and conversely, a proper bowel prep may alleviate chronic pain, suggesting functional bowel symptoms. Finding melanosis coli (hyperpigmented mucosa) will suggest the prolonged laxative use that often accompanies chronic constipation. Symptomatic patients over 50 years might benefit from full colonoscopy, as it is a better test to screen for neoplasia, but any pertinent information regarding their symptoms should be available in the left colon. Note that when lower endoscopy is used to evaluate chronic diarrhea, full colonoscopy with biopsies is needed to rule out microscopic colitis, which sometimes occurs only in the right colon. Similarly, full colonoscopy is needed in the patient infected with human immunodeficiency virus who presents with chronic diarrhea.

## PROCEDURAL RISKS

### Discomfort

Some discomfort should be anticipated by the patient, but it is important to reiterate this point. Patients need to know that the endoscopist is attuned to their subjective experience, will try to minimize painful stimuli, and will respond to the patients' input during the test. Air insufflation and scope looping are the primary sources of pain and both these sources can be ameliorated. Anal pain due to fissure or hemorrhoids should be managed proactively with anesthetic lubricant if the preprocedural rectal exam suggests the need.

### Bleeding

Mucosal scratches due to the endoscope are rare and seldom bleed. However, friable mucosa associated with colitis or uncorrected coagulopathy may bleed slightly with even the mildest scope trauma. The removal of polyps with forceps (removal of larger polyps with other instruments is rarely undertaken during sigmoidoscopy and is discussed elsewhere) almost never leads to clinically significant bleeding, although rectal polypectomies may result in a small amount of blood with the stool over the subsequent few hours. In colonoscopy studies, bleeding rates for purely diagnostic examinations are approximately 0.02% and the risk for sigmoidoscopy is likely comparable. The bleeding risk for colonoscopic polypectomy cases is significantly higher, but large polyps are not removed during sigmoidoscopy. The added risk with forceps-mediated polypectomies is not known, but unlikely to be much higher than for purely diagnostic studies, based on common experience.

### Perforation

Perforation rates for flexible sigmoidoscopy are roughly 1 in 10,000. The risk for this complication is lower than during colonoscopy for several reasons: less scope is inserted, less air is insufflated, few polypectomies utilizing cautery are performed, the thin-walled cecum will become less inflated than during colonoscopy, and the awake patient will complain of the significant looping or distension that increases risk of perforation. Although event rates are low with sigmoidoscopy, each procedure should be carried out with the utmost caution. Every patient must be warned of the risk for perforation with endoscopy.

### Infection

The risk of infection related to sigmoidoscopy may be more theoretical than practical. In the past, much was written about postendoscopic bacteremia caused by bowel-flora translocation via a thin, distended bowel wall. Studies have demonstrated bacteremia occurring after sigmoidoscopy, with the greatest concern being for patients who could not cleanse the portal blood, i.e., cirrhotics and patients with vascular prostheses. Yet, the data have never clearly shown a clinically significant infectious risk with sigmoidoscopy, although rare cases may still occur.

### Chemically Induced Colitis

Colitis can occur as a result of incompletely rinsed disinfectants. Hydrogen peroxide and glutaraldehyde are commonly used for disinfecting endoscopes. If these agents are not thoroughly washed off the instrument shaft and channels, they can subsequently come in contact with the next patient in whom the instrument is used. These chemicals will cause a self-limited colitis with patients experiencing postprocedural cramping, tenesmus, and bleeding per rectum. Therapy is supportive, but preemptive avoidance via proper endoscopic cleaning and rinsing techniques is most important.

### Vasovagal Reaction

It is not uncommon for anal stimulation with the endoscope and/or colonic distension with air to trigger a vasovagal reaction. The endoscopist should be aware of this and realize that air suction and scope withdrawal can correct the condition. Some conversation between the endoscopist and the patient during the procedure allows the latter to report suggestive symptoms.

### Other Risks

There are other potential complications of sigmoidoscopy, such as postpolypectomy syndrome, pneumatosis coli, ischemic colitis, electrolyte abnormalities, and "mini-perforation." These are rare with sigmoidoscopy. Similarly, risks associated with conscious sedation will not be discussed here.

## CONTRAINDICATIONS

### Absolute Contraindications

#### *Suspected Severe or Toxic Colitis, Including Acute Diverticulitis*

When the bowel wall is severely inflammed it may become thin and particularly susceptible to perforation. Sigmoidoscopy should not be performed in this setting, unless it is absolutely necessary for diagnosis and management. In that circumstance, it should be performed only by an experienced endoscopist, with care taken to avoid advancing the sigmoidoscope beyond the level of inflammed mucosa. If there is clinical or radiological evidence of toxic megacolon, sigmoidoscopy should not be performed.

#### *Suspected Perforation*

A small tear in the bowel will surely enlarge with air insufflation, potentially leading to more leakage of bowel contents into the peritoneal cavity. Some patients with small perforations may be able to avoid surgery if they "self-seal" with overlying omentum, a process likely to be disrupted with added bowel distension. Similarly, the patient who will need an operation anyway will likely need a lengthier surgery after endoscopy creates a larger hole with more spillage.

#### *Suspected Bowel Obstruction*

In an obstruction, the dilated bowel has increased wall tension. The inevitable insufflation that occurs during endoscopy may lead to hyperbaric trauma with perforation and peritoneal soilage. Bowel obstruction should be viewed as a surgical emergency and never as an endoscopic question awaiting an answer. That being said, there are times when a known sigmoid volvulus may be amenable to endoscopic reduction (usually after gastrograffin enema has failed to do so) or persistent pseudo-obstruction may benefit from endoscopic placement of a decompression tube. These are procedures with significant risks for perforation, generally performed to postpone surgical intervention. Such procedures should be performed only by the most experienced therapeutic endoscopist and with surgical backup.

#### *Agitated Patient*

If a patient is overly anxious, is belligerent, or otherwise cannot lie still for an examination, the risk of traumatic injury outweighs the benefits of the procedure.

### Relative Contraindications

#### *Acute Illness*

Sigmoidoscopy is usually an elective procedure and, as such, should await a patient's recovery to reasonable health. Even in skilled hands, sigmoidoscopy can be somewhat uncomfortable and its risks, although usually negligible, will rise in the patient who is already uncomfortable or in any way prone to hemodynamic instability.

#### *Coagulopathy*

The risk of bleeding with sigmoidoscopic examination is quite low and an examination usually can be performed safely in the anticoagulated patient, although biopsies might well be avoided in such subjects.

#### *Colonoscopy Is Preferable Test*

A patient who ought to have colonoscopy for reasons of symptoms, colorectal cancer screening, or surveillance should not undergo sigmoidoscopy as it would not obviate the need for complete colonic evaluation.

#### *Recent Bowel Surgery*

Within 5 to 7 days after bowel surgery, hyperbaric trauma, such as that resulting from endoscopic insufflation, should be avoided to reduce risk of anastomotic breakdown.

#### *Recent Myocardial Infarction*

Within 3 weeks of acute myocardial infarction, all endoscopy should be limited to emergent cases. Most of the risk relates to administration of conscious sedation and its potential hemodynamic consequences. Yet, even without sedation, sigmoidoscopy can cause tachycardia or vagal reaction, which could incite ischemia in the

recently injured myocardium. If endoscopy must be performed, insufflation should be minimized and electrocardiographic monitoring is advisable.

### *Pregnancy*

Studies have shown that sigmoidoscopy is safe during each trimester of pregnancy. That being said, there is a theoretical risk of placental abruption, so purely elective procedures, as to work up minor bleeding or altered bowel habits, might best be postponed until postpartum. However, more pressing issues, such as ongoing rectal bleeding or colitis of uncertain cause may be safely pursued endoscopically, without delay.

## SIGMOIDOSCOPISTS

The number of sigmoidoscopies performed has increased with the widening appreciation of colon cancer screening. And even so, a nationwide 1997 survey revealed that only 30% of potential candidates in the United States were having screening flexible sigmoidoscopies. Although screening colonoscopy has become accepted by most third-party payers, the number of skilled colonoscopists, mostly trained gastroenterologists, is insufficient to meet the needs of the populace. Therefore, sigmoidoscopy will continue to play a role in screening until a less invasive, inexpensive, colorectal cancer screening test replaces it. Until that test is found and accepted, sigmoidoscopy needs to be performed by a wide cadre of professionals. Studies have demonstrated that internists, general practitioners, physician assistants, and nurse practitioners can properly perform the test. In order to allow more patients to benefit from colorectal cancer screening, flexible sigmoidoscopy training programs for nongastroenterologist health care providers should be promoted.

## See Also the Following Articles

**Colonoscopy • Colorectal Adenocarcinoma • Colorectal Adenomas • Colorectal Cancer Screening • Endoscopy, Complications of • Lower Gastrointestinal Bleeding and Severe Hematochezia •** Virtual Colonoscopy

## Further Reading

Cotton, P., and Williams, C. (1996). "Practical Gastrointestinal Endoscopy," 4th Ed. Blackwell Science Inc., Cambridge, MA.

Lieberman, D., and Weiss, D. (2001). One-time screening for colorectal cancer with combined fecal occult-blood testing and examination of the distal colon. *N. Engl. J. Med.* 345, 555–560.

McCallion, K., Mitchell, R., Wilson, R., *et al.* (2001). Flexible sigmoidoscopy and the changing distribution of colorectal cancer: Implications for screening. *Gut* 48, 522–525.

Miller, B. (2001). A review of sigmoidoscopy. *In* "An Atlas of Sigmoidoscopy and Cystoscopy" (B. Miller, ed.), The Encyclopedia of Visual Medicine Series, Parthenon, New York.

Painter, J., Saunders, D., Bell, G., *et al.* (1999). Depth of insertion at flexible sigmoidoscopy: Implications for colorectal cancer screening and instrument design. *Endoscopy* 31, 227–231.

Ransohoff, D., and Sandler, R. (2002). Screening for colorectal cancer. *N. Engl. J. Med.* 346, 40–44.

Shapiro, J., Seeff, L., and Nadel, M. (2001). Colorectal cancer-screening tests and associated health behaviors. *Am. J. Prev. Med.* 21, 132–137.

Van Rosendaal, G., Sutherland, L., Verhoef, M., *et al.* (2000). Defining the role of fiberoptic sigmoidoscopy in the investigation of patients presenting with bright red rectal bleeding. *Am. J. Gastroenterol.* 95, 1184–1187.

Waye, J., Kahn, O., and Auerbach, M. (1996). Complications of colonoscopy and flexible sigmoidoscopy. *Gastrointest. Endosc. Clin. North Am.* 6, 343–377.

# Sinusoidal Obstruction Syndrome (Hepatic Venoocclusive Disease)

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**conditioning regimen** Procedures performed in preparation for stem cell transplantation, which consists of high-dose chemotherapy with or without total body irradiation.

**hematopoietic stem cell transplantation** A procedure formerly known as bone marrow transplantation.

**pyrrolizidine alkaloids** Plant-derived alkaloids that may cause sinusoidal obstruction syndrome.

**sinusoidal obstruction syndrome** A nonthrombotic obstruction of the hepatic circulation with subsequent centrilobular sinusoidal fibrosis and, often, fibrotic obliteration of hepatic venules. Formerly known as hepatic venoocclusive disease.

**Sinusoidal obstruction syndrome (SOS) is a disease of the hepatic circulation that leads to parenchymal dysfunction. SOS is caused by exposure to plant toxins or to drugs with or without concurrent total body irradiation. In North America and Western Europe, SOS occurs mainly due to the preparative conditioning regimen for stem cell transplantation. Although 70 to 85% of patients with SOS survive, severe SOS is almost uniformly fatal. There is currently no specific therapy for SOS with good efficacy.**

## ETIOLOGY

The earliest case reports of sinusoidal obstruction syndrome (SOS) in humans were of individuals in South Africa who ingested teas containing pyrrolizidine alkaloids, so-called "bush tea disease." Bras *et al.* in Jamaica coined the name hepatic venoocclusive disease in response to the most prominent histologic feature, notably the narrowing or obliteration of intrahepatic venules. In many non-Western nations, ingestion of teas or of food sources contaminated by pyrrolizidine alkaloids may still be the most common cause of the disease (see Table I). However, in North America and Europe, the most common cause is high-dose myeloablative chemotherapeutic regimens, alone or in conjunction with total body irradiation, used in preparation for hematopoietic stem cell transplantation. SOS is also seen in renal and liver transplant patients and this is attributed to long-term azathioprine therapy. Chemotherapeutic agents that are associated with SOS at conventional doses include gemtuzumab ozogamicin, actinomycin D, dacarbazine, 6-thioguanine, cytosine arabinoside, mithramycin, and urethane. Given the increased use of herbal remedies, sporadic cases of SOS may be seen due to teas that contain pyrrolizidine alkaloids, notably teas from *Crotalaria*, *Senecio*, *Heliotropium*, *Comfrey*, *Gordolobo yerba*, *Ilex*, and *Mate*. Hepatic irradiation in excess of 30 to 35 Gy in adults causes radiation-induced liver disease, a liver disease that shares some of the features of SOS.

In other intrinsic liver diseases, progressive parenchymal dysfunction may eventually cause portal hypertension. Sinusoidal obstruction syndrome differs in that

TABLE I Causes of Sinusoidal Obstruction Syndrome

| |
|---|
| Chemotherapy |
| Myeloablative regimens (stem cell transplantation) |
| Cyclophosphamide–total body irradiation |
| Busulfan–cyclophosphamide |
| BCNU–cyclophosphamide–etoposide[a] |
| Carboplatin–cyclophosphamide–BCNU |
| Busulfan–melphalan |
| Conventional dose chemotherapy |
| Gemtuzumab ozogamicin |
| Actinomycin D |
| Dacarbazine |
| Cytosine arabinoside |
| 6-Thioguanine |
| Carmustine |
| Lomustine |
| Urethane |
| Indicine *N*-oxide |
| Pyrrolizidine alkaloids |
| *Crotalaria* |
| *Senecio* (Adenostyles) |
| *Heliotropium* |
| *Comfrey* |
| *Gordolobo yerba* |
| *Ilex* |
| *Mate* |
| Azathioprine immunosuppression |

[a] BCNU, carmustine.

 

it is a disease of the hepatic circulation that may cause parenchymal dysfunction. The circulatory impairment is a nonthrombotic obstruction at the level of the sinusoids and involvement of central veins and venules is more common with more severe disease. The change in name from hepatic venoocclusive disease to sinusoidal obstruction syndrome is based on the recognition that the disease is initiated in the hepatic sinusoids and that the clinical signs and symptoms can occur without involvement of the hepatic venules.

## CLINICAL FEATURES OF SOS AFTER STEM CELL TRANSPLANTATION

It would be too cumbersome to try to describe SOS in the different settings. The rest of this article will therefore focus on SOS in patients treated with myeloablative chemotherapeutic regimens. It should be noted that SOS due to long-term ingestion of pyrrolizidine alkaloids has a more chronic course than that due to toxicity from short-term exposure to chemotherapy.

### Incidence

The reported incidence of SOS varies from 0 to 50% in patients undergoing stem cell transplantation for malignancies. This wide range is largely due to differences in conditioning regimens, i.e., chemotherapeutic regimens used prior to stem cell transplantation. Other important variables relate to patient selection criteria: the risk of SOS is increased in patients undergoing a second transplant, in patients with malignancy not in remission, in patients with chronic hepatitis C or fibrotic liver disease, or in patients with lower performance status. There has been a decline in recent years in the incidence of SOS with the application of strategies to reduce the risk of this syndrome.

### Diagnosis

The hallmark features of SOS are tender hepatomegaly, weight gain due to fluid retention, and hyperbilirubinemia. The diagnosis is usually made based on published clinical criteria (Table II). The differential diagnosis includes (hyper)acute graft-versus-host disease, cholestasis associated with sepsis or cyclosporine therapy, hemolysis, congestive heart failure, and decompensated chronic viral hepatitis. Combinations of illnesses that occur posttransplantation may be particularly difficult to distinguish from SOS, e.g., sepsis complicated by cholestasis and renal insufficiency.

Ultrasound may demonstrate features consistent with SOS and may exclude other causes, but cannot establish the diagnosis. Thus, ultrasound may demonstrate hepatomegaly, ascites, lack of biliary dilation, and absence of tumor invasion in the parenchyma or the hepatic vasculature. Early in SOS there may be attenuation of hepatic venous flow and later in the disease there may be reversal of portal flow, but prospective studies of these features did not show them to be diagnostic.

The most useful additional diagnostic tool is transvenous liver biopsy, which will both provide biopsy material and allow measurement of the hepatic venous pressure gradient. Thrombocytopenia due to the conditioning therapy will restrict the use of percutaneous liver biopsy, but the transvenous approach can be safely performed with platelet counts as low as 30,000/mm$^3$. A hepatic venous pressure gradient of greater than 10 mm Hg is highly specific for SOS in stem cell transplantation patients.

### Prognosis

It is likely that all or most patients who undergo myeloablative stem cell transplantation sustain some degree of liver damage. By definition, patients with mild SOS recover without therapy. Moderate SOS may require diuretics or pain medication and the majority of patients survive, whereas severe SOS is almost universally fatal. Patients with severe SOS most commonly die from multiorgan failure, i.e., renal and cardiopulmonary failure. Death usually occurs 30 to 60 days after conditioning therapy, although the outcome is often evident by day 20.

Published case fatality rates for SOS vary widely. Based on findings from several large studies, the case fatality rate for SOS after cyclophosphamide-containing regimens seems to be approximately 30%, but may be approximately 15% for SOS caused by other alkylating

**TABLE II Clinical Diagnostic Criteria for SOS in Stem Cell Transplantation Patients**

| Seattle criteria | Baltimore criteria |
|---|---|
| At least 2 of 3 findings within 20 days of stem cell transplantation:<br>Bilirubin > 2 mg/dl<br>Hepatomegaly or right upper quadrant pain<br>> 2% weight gain due to fluid retention | Elevated bilirubin (> 2 mg/dl) plus 2 of 3 clinical findings:<br>Tender hepatomegaly<br>> 5% weight gain<br>Ascites |

agents. There are published graphs that can help predict the outcome for SOS due to cyclophosphamide-containing regimens. Alanine aminotransferase levels greater than 750 U/liter are associated with a poor prognosis. Other predictors of poor outcome include higher hepatic venous pressure gradient, portal vein thrombosis, doubling of baseline serum creatinine, and declining oxygen saturation.

## PREVENTION OF SOS

As with any form of drug-induced liver disease, the best approach to primary prevention is to avoid the therapy in those at highest risk. Those at highest risk include patients with hepatitis C, extensive hepatic fibrosis, or cirrhosis, individuals who have previously received myeloablative regimens, patients with malignancy not in remission, and patients with a previous episode of SOS.

There are several strategies that may reduce the risk of SOS. Nonmyeloablative regimens that do not contain hepatotoxic drugs are one possibility. Myeloablative regimens may be modified to reduce risk. The value of therapeutic monitoring with dosage adjustment of busulfan is controversial, given the inconsistent outcome of several studies. Administration of cyclophosphamide before busulfan may be protective. Decreased doses of total body irradiation are associated with a lower incidence of SOS. It is controversial whether modification of the radiation technique reduces the risk. The source of irradiation may be important, since cobalt sources and linear accelerator differ in the dose rate. Avoidance of cyclophosphamide-containing regimens in patients at risk for SOS is another possible approach. Although some of the approaches listed above may reduce the risk of SOS, this needs to be weighed against the potential for increased risk of graft-versus-host-disease, poor engraftment, or unsuccessful treatment of the underlying malignancy.

Heparin infusion or low-molecular-weight heparin is used routinely in many centers, but there are no randomized studies that demonstrate that this successfully prevents fatalities from SOS. Urodeoxycholic acid, prostaglandin E1, and pentoxifylline have also been tried, but the preponderance of evidence does not support the efficacy of prevention by these drugs.

## MANAGEMENT OF SOS

### Supportive Care

There is currently no specific and satisfactory therapy for SOS. Conventional supportive care is used to manage fluid and electrolyte balance and ascites. Renal and pulmonary failure may necessitate hemodialysis and mechanical ventilation, but outcome will more likely reflect the severity of the underlying liver disease.

### Pharmacologic Therapy

The combination of tissue plasminogen activator and heparin is beneficial in approximately 30% of patients with severe SOS. However, in the largest series to date, patients with renal and pulmonary failure did not benefit. Patients at risk for intracerebral or pulmonary hemorrhage should be excluded from consideration for this approach.

Defibrotide is an experimental drug that has shown promise in uncontrolled trials. Various other pharmacologic approaches have been described in case reports, but have not been confirmed in clinical trials.

### Transjugular Intrahepatic Portosystemic Shunt

Transjugular intrahepatic portosystemic shunt (TIPS) has been used in these patients with improvement in ascites. However, outcome of SOS is dependent on the underlying liver disease, which is not altered by TIPS placement.

### Liver Transplantation

Liver transplantation is not usually a consideration for patients who undergo stem cell transplantation for malignancy. SOS is rare in patients who undergo transplantation for nonmalignant indications, but liver transplantation for SOS should certainly be considered in patients with a favorable prognosis for their underlying disease.

### See Also the Following Articles

Cirrhosis • Hepatic Circulation • Hepatitis C • Liver Transplantation

### Further Reading

Bearman, S. I. (1995). The syndrome of hepatic venoocclusive disease after marrow transplantation. *Blood* 85, 3005–3020.

Bearman, S. I., Anderson, G. L., *et al.* (1993). Venoocclusive disease of the liver: Development of a model for predicting fatal outcome after marrow transplantation. *J. Clin. Oncol.* 11, 1729–1736.

Brooks, S. E. H., Miller, C. G., *et al.* (1970). Acute venoocclusive disease of the liver. *Arch. Pathol.* 89, 507–520.

Carreras, E. (2000). Venoocclusive disease of the liver after hematopoietic cell transplantation. *Eur. J. Haematol.* 64, 281–291.
DeLeve, L. D. (2002). Cancer chemotherapy. *In* "Drug-Induced Liver Disease" (N. Kaplowitz and L. D. DeLeve, eds.), Chap. 24., pp. 593–632. Dekker, New York.
DeLeve, L. D., Shulman, H. M., *et al.* (2002). Toxic injury to hepatic sinusoids: Sinusoidal obstruction syndrome (venoocclusive disease). *Semin. Liver Dis.* 22, 623–638.
Rollins, B. J. (1986). Hepatic venoocclusive disease. *Am. J. Med.* 81, 297–306.

# Sjögrens Syndrome

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**autoantibodies** Antibodies directed against a normal cellular component.
**cevimeline** Cholinergic drug that stimulates secretion of most exocrine glands, including lacrimal and salivary glands.
**keratoconjunctivitis sicca** Dry eye and associated symptoms due to the absence of the aqueous component of tears.
**lacrimal glands** The glands producing tear fluids that bathe the surface of the eye (cornea).
**pilocarpine** Cholinergic drug that stimulates secretion of most exocrine glands, including lacrimal and salivary glands.
**rheumatoid factor** An autoantibody directed against immune globulin that is present in rheumatoid arthritis.
**T cells** Thymus-derived lymphocytes.
**xerostomia** Dry mouth due to the absence of salivary secretions.

**Sjögrens syndrome (SS) is a debilitating, systemic, autoimmune disorder with prominent exocrinopathy that has been described as an "epithelitis." SS may be categorized as primary or secondary. In secondary SS, the disorder coexists with other autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, scleroderma, polymyositis, and polyarteritis nodosa. Salivary and lacrimal gland involvement is typical of SS and is associated with decreased production of saliva and tears. Other epithelial components of the body are commonly involved, including the skin, as well as the urogenital, respiratory, and gastrointestinal tracts. Systemic autoimmune manifestations include synovitis, neuropathy, vasculitis, and autoantibodies, particularly antinuclear antibodies, anti-SSA, and anti-SSB, as well as rheumatoid factor. Immunoglobulin levels are frequently elevated. SS is associated with an increased risk of lymphoma, especially mucosal-associated lymphoid tissue lymphomas of B-cell lineage.**

## EPIDEMIOLOGY AND CLASSIFICATION CRITERIA

Primary Sjögrens syndrome (SS) affects 0.3 to 4.8% of the population and appears to increase in frequency with age. The physician-diagnosed incidence is 4 per 100,000 population per year. Females outnumber males by 9 : 1. Although the peak incidence occurs in midlife, SS may occur at any age. Onset is often insidious and diagnosis may be delayed for years.

Various classification criteria have been proposed for SS. These criteria have generally included keratoconjunctivitis sicca, xerostomia, and autoantibodies. American European Consensus criteria are currently the most widely accepted. The recently revised criteria are shown in Table I. The rules for applying the criteria are shown in Table II.

## PATHOGENESIS

The pathogenesis of SS remains unknown. Viruses that can cause disease in salivary glands, such as cytomegalovirus, hepatitis C, and the retroviruses human T-cell lymphotropic virus-1 and human immunodeficiency

TABLE I Revised American–European Classification Criteria for Sjögren's Syndrome

I. **Ocular symptoms**: A positive response to one or more the questions below:
   1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?
   2. Do you have a recurrent sensation of sand or gravel in the eyes?
   3. Do you use tear substitutes more than 3 times a day?

II. **Oral symptoms**: A positive response to one or more of the questions below:
   1. Have you had a daily feeling of dry mouth for more than 3 months?
   2. Have you had recurrently or persistently swollen salivary glands as an adult?
   3. Do you frequently drink liquids to aid in swallowing dry food?

III. **Ocular signs**: Objective evidence of eye involvement defined as a positive result for one or both of the two tests below:
   1. Positive Schirmer's I test, performed without anesthesia ($\leq 5$ mm wetting in 5 min)
   2. Positive Rose Bengal or other ocular dye staining with Van Bijsterveld score $\geq 4$.

IV. **Histopathology**: In minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialoadenitis, evaluated by an expert histopathologist, with a focus score $\geq 1$, defined as a number of lymphocytic foci that are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes per 4 $mm^2$ of glandular tissue.

V. **Salivary gland involvement**: Objective evidence of involvement indicated by a positive result for at one or more of the diagnostic tests below:
   1. Unstimulated whole salivary flow ($\leq 1.5$ ml in 15 min)
   2. Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitary, or destructive pattern), without evidence of obstruction in the major ducts.
   3. Salivary scintigraphy showing delayed uptake, reduced concentration, and/or delayed excretion of tracer.

VI. **Autoantibodies**: Presence in the serum of the following autoantibodies:
   1. Antibodies to Ro(SSA) or La(SSB) antigens, or both.

virus type 1, have been considered as possible triggers for SS. However, no causative organism has been found.

Hormonal factors, such as relatively low levels of androgens, may explain the preponderance of females with SS. Also, hypofunction of the hypothalamic–pituitary–adrenal axis has been described in SS.

Genetic factors may also have a role in SS. An increased prevalence of SS and autoantibodies, particularly anti-Ro/SSA, occurs in family members, and HLA-DR3, HLA-DQ2, and other genetic markers are associated with SS.

Focal mononuclear cell infiltration of exocrine tissues and the presence of autoantibodies, especially anti-Ro/SSA, anti-La/SSB, and rheumatoid factor, are key features of SS. The periductal infiltrate in the salivary and tear glands consists mainly of T cells with fewer B cells, macrophages, and mast cells. Most of the T cells are $CD4^+$ helper cells with the memory phenotype $CD45RO^+$ and appear to be resistant to apoptosis despite increased expression of Fas. Apoptosis may be blocked by the suppressor proto-oncogene Bcl-2, allowing autoreactive cells to persist in the exocrine tissues.

Salivary and lacrimal gland epithelial cells in SS show increased HLA-DR antigen expression, which allows these cells to present antigens, including autoantigens, to the CD4 T cells. Cellular interactions can result in the production of cytokines. Proinflammatory cytokines interleukin-1β (IL-1β), IL-6, and tumor necrosis factor α tend to be produced by epithelial cells, whereas IL-10 and interferon-γ

TABLE II Revised Classification Rules

*Primary SS*

In the absence of any potentially associated disease, primary SS may be defined as follows:

1. Presence of *any 4 out of the 6 items* is indicative of primary SS, as long as either item 4 (histopathology) or 6 (serology) is positive.
2. The presence of *any 3 of the 4 objective criteria items* (i.e., items III, IV, V, VI in Table I).
3. A classification tree procedure may be used as a valid alternative method for classification.

*Secondary SS*

For patients who have a potentially associated disease (e.g., another well-defined connective tissue disease), the presence of *item I or item II plus any two from among items III, IV, and V* from Table I may be considered as indicative of secondary SS.

Exclusions

History of head and neck irradiation, preexisting lymphoma, sarcoidosis, graft-versus-host disease, hepatitis C or human immunodeficiency virus infection, use of anticholinergic drugs (within 4 half-lives of taking the drug).

(IFN-γ) are produced mostly by infiltrating T cells. IFN-γ increases HLA-DR and La/SSB expression by glandular epithelial cells and IL-10 can induce B-cell proliferation. In SS, B-cell activation is typical and may progress toward B-cell lymphoid malignancy.

Activated B cells in SS produce increased amounts of immunoglobulins with autoantibody reactivity for immunoglobulin G (IgG) (rheumatoid factor), Ro/SSA, and La/SSB. Also, B cells produce antibodies targeting the muscarinic M3 receptor. In SS, muscarinic (acetylcholine) receptor blockade in exocrine tissue would inhibit the production of secretions. Since complete destruction of the salivary tissue is rarely seen in salivary gland biopsies of SS patients, it has been suggested that cytokines may interact directly with epithelial cells or autoantibodies, other than those directed against muscarinic M3 receptors. For example, interference with the nerve supply might also decrease secretions in a manner disproportionate to the level of tissue destruction.

## CLINICAL FEATURES

Typical manifestations of SS are oral and ocular symptoms and signs of dryness, the presence of autoantibodies, especially anti-Ro/SSA and anti-La/SSB antibodies, and a positive labial salivary gland biopsy.

### Eyes

The precorneal tear film has three layers, progressing outward from the corneal surface: mucus, water (aqueous), and oil. The dry eyes of SS are due to aqueous tear deficiency, which, however, may exist in the absence of SS because of other lacrimal gland diseases, lacrimal duct obstruction, and loss of reflex tearing. The aqueous tear deficiency of SS produces symptoms of ocular irritation, particularly a gritty sensation in the eye, and a positive Schirmer's test and the finding of ocular surface damage on the slit lamp examination with increased uptake of ocular dyes are observed. The diagnostic eye tests are shown in Table I.

### Mouth

SS patients often experience a sensation of decreased saliva, oral dryness on eating, a need to drink liquids to facilitate swallowing of dry foods, spicy food intolerance, altered taste, and burning mouth. Speech difficulties interfere with social interactions and functioning in the workplace. More than 400 medications are known to be associated with dry mouth symptoms, including drugs commonly used in the treatment of hypertension, insomnia, and depression. Head and neck radiation used to treat tumors produces severe oral dryness. Patients treated with radioactive iodine for thyroid disorders may later present with oral dryness, since the isotope tends to concentrate in the salivary glands. Dental erosions and caries are common, especially on the incisal edges of the teeth and at the gingival margins. A dry sticky mucosa and furrowed tongue are often seen. The mucosa often displays the typical erythema and white patches associated with candidiasis. Decreased or absent saliva pooling is often present. Swallowing difficulties may be evaluated by barium swallows or ultrasound studies.

Major salivary gland swelling and tenderness may occur. The parotid gland swelling displaces the earlobe and extends downward over the angle of the jaw. Medial to the angle of the jaw, submandibular salivary gland swelling may be seen or, more often, palpated. The swelling may transient or chronic and is often recurrent, which distinguishes it from mumps.

### Other Clinical Features

#### *Gastrointestinal*

In addition to the oral manifestations mentioned above, SS is associated with dysphagia, esophageal dysmotility, and esophageal webs. Lymphoid infiltration may occur in the gastrointestinal tract. Chronic atrophic gastritis may give rise to dyspeptic symptoms, including nausea and epigastric discomfort. *Helicobacter pylori* has been suspected to play a role in the gastrointestinal manifestations of SS, but evidence involving normal population controls is not available. The extent to which small and large bowel involvement occurs in SS is unclear. However, patients frequently complain of bloating and constipation. Patients on muscarinic agonists such as pilocarpine or cevimeline may complain of abdominal cramping and may have an increase in the frequency of bowel movements or diarrhea. Pancreatic involvement may occur, but is usually subclinical. Primary biliary cirrhosis may be associated with SS. Hepatitis C has emerged as an important infection that mimics SS, including the salivary gland lymphocytic infiltration, decreased saliva production, hypergammaglobulinemia, and vasculitis. However, such patients generally have no anti-SSA or anti-SSB antibodies. It is therefore important to rule out hepatitis C in individuals who appear to have SS.

#### *Skin*

Dry skin affects approximately half of SS patients. Sweating may be decreased. Dry skin and peripheral

neuropathy may result in pruritis. Scratching repeatedly may produce increased hyperpigmentation, excoriations, and lichenification. Also, some patients may develop palpable or nonpalpable purpura and petechiae, most often on the lower extremities, in showers of lesions lasting several days. The lesions, on microscopic examination, are consistent with either leucocytoclastic vasculitis or mononuclear inflammatory vasculopathy.

### *Thyroid*

Thyroid disorders, most often hypothyroidism, are common in SS patients. This may reflect the prevalence of such thyroid disease in individuals of a similar age in the general population or could be a true association of autoimmune thyroiditis with SS.

### *Respiratory*

Most SS patients with pulmonary involvement do not develop progressive disease. A dry cough is experienced by many SS patients and probably reflects tracheal dryness and decreased mucus production. The cough may also be related to hyperreactive airways in both primary and secondary SS. Also, mild interstitial pulmonary disease and rheumatoid-like pulmonary nodules may occur in SS.

### *Rheumatologic*

Manifestations may include low-grade fever, fatigue, lymphadenopathy, myalgias, arthralgias, and symmetrical, nondeforming polyarthritis, which is responsive to standard antirheumatic therapies.

### *Neurologic*

Peripheral neuropathy is not uncommon in SS, is most notable in the lower limbs, and is most often sensory. Autonomic neuropathy also occurs. Also, the central nervous system involvement has been reported with lesions noted in imaging studies.

### *Hematologic*

Lymphoid malignancy is the most important hematologic complication of SS. Up to a 44-fold increase in the risk of B-cell lymphomas has been reported in SS patients. Non-Hodgkin's lymphomas of mucosa-associated lymphoid tissues are the most common in SS patients, and often salivary glands and cervical lymph nodes are involved.

### *Reproductive*

Women often experience vaginal dryness, which may be the first symptom of SS and is commonly associated with dyspareunia. Anti-SSA (Ro) antibodies occur in SS, raising the possibility of congenital heart block, although the frequency is low.

### *Renal*

Symptoms consistent with irritable bladder are not uncommon. Urinary frequency may result from increased fluid intake to alleviate oral dryness, as well renal abnormalities associated with diminished ability to concentrate urine (hyposthenuria). Renal abnormalities include hyposthenuria in approximately half the cases, distal renal tubular acidosis in approximately 15% of cases, as well as nephrocalcinosis, renal stones, and less often interstitial nephritis and glomerular disease. Urine pH is usually in excess of 5.5 in renal tubular acidosis. The associated systemic acidosis results in mobilization of calcium from bone, promoting osteoporosis and resulting in hypercalciuria. Urinary citrate, which normally complexes a substantial proportion of urine calcium, is decreased. This raises the risk of calcium phosphate stone formation. In approximately half of SS cases, tubular proteinuria may occur. Glomerular disease affects approximately 2% of the patients, tends to be associated with cryoglobulins, and occurs more often in those with longer disease duration.

## LABORATORY FEATURES

SS is associated with rheumatoid factor (90%), anti-Ro/SSA or anti-La/SSB (50–90%), and often hypergammaglobulinemia. Antinuclear antibodies occur in approximately 80% of cases. The 52 kDa Ro is more often associated with SS, whereas 60 kDa Ro appears to be more frequent in systemic lupus erythematosus. Anti-Ro/SSA antibodies are associated with systemic manifestations of the disease, including anemia, leukopenia, thrombocytopenia, purpura, cryoglobulinemia, hypocomplementemia, lymphadenopathy, and vasculitis. Other autoantibodies have been recognized in SS, including those directed against carbonic anhydrase, pancreatic antigen, α-fodrin, 97 kDa Golgi complex, mitotic spindle apparatus, M3 muscarinic acetylcholine receptors, and Fcγ receptors. These latter autoantibodies are not currently used to diagnose or monitor the disease.

## DIAGNOSIS

The diagnosis of SS may be made by applying the published classification criteria. The differential diagnosis for SS includes the disorders listed as exclusions in Table II.

## TREATMENT

### Patient Education and Self-Care

The patient will benefit from education about the disease and assistance in developing strategies for self-management as well as for coping with physical, mental, and social challenges associated with their condition.

### Sicca Symptoms

#### *Keratoconjunctivitis Sicca*

Treatment of dry eyes includes tear replacement and conservation, as well as topical ocular and systemic medications. Artificial tears are instilled as eyedrops to ameliorate symptoms. Preservative-free preparations are best to avoid irritation, ocular surface damage, and allergic reactions. The use of small individual dispensers minimizes the risk of bacterial growth and infection.

Hydroxypropylcellulose pellets inserted under the lower eyelids may be used to prolong the effects of artificial tears. Ointments are used at night, since they are viscous and may interfere with vision. Topical steroids or cyclosporine may be beneficial in the treatment of keratoconjunctivitis sicca.

Systemic secretogogues such as pilocarpine and cevimeline may improve ocular symptoms. Typically, pilocarpine is given in a dosage of 5 mg orally four times a day, and the total daily dose usually does not exceed 30 mg. Adverse effects include increased perspiration, feeling hot and flushed, as well as symptoms associated with increased bowel and bladder motility. Caution must be exercised in the presence of bronchospasm. Some patients who experience adverse effects may benefit from one to three 5 mg doses per day to ameliorate symptoms at the most troublesome time of day. Cevimeline has recently been approved for the treatment of dry mouth in SS at a dosage of 30 mg orally three times daily. Like pilocarpine, it is a muscarinic agonist that increases production of saliva and possibly tears and other secretions. The drug is contraindicated for individuals with uncontrolled asthma, iritis, and narrow angle glaucoma. The role of systemic, immunomodulatory treatment for the ocular manifestations of SS remains unclear.

#### *Xerostomia*

Frequent dental care, an appropriate diet, limiting sugar intake, daily topical fluoride use, antimicrobial mouth rinses, and exchanging medications that promote oral dryness or its complications for more appropriate ones may limit the development of caries in patients with reduced salivary flow. Artificial saliva, lubricants, and sugar-free chewing gum or candies may ameliorate oral dryness. Oral moisturizers and lubricants, as well as dietary modifications, may improve dysphagia. Sicca symptoms may be improved by using humidifiers. As in the treatment of ocular dryness, secretagogues such as pilocarpine or cevimeline may increase secretions in patients with sufficient exocrine tissue.

Oral candidiasis commonly complicates the dry mouth of SS and is treated by the use of oral troches or vaginal suppositories of antifungal agents, such as Nystatin or clotrimazole. Angular cheilitis may require topical antifungal agents. Bacterial parotitis should be treated with warm compresses, massage of the parotid gland, and, if necessary, antibiotics.

### Systemic Manifestations

Immunomodulatory drugs can be used to treat systemic or exocrine autoimmune and inflammatory manifestations. Hydroxychloroquine is often given for milder systemic manifestations of autoimmune disorders, such as fever, rashes, and arthritis. It remains unclear whether hydroxychloroquine is effective for the exocrine component of the disease, although serological measures improve in SS patients on this drug. Methotrexate, prednisone, azathioprine, and other immunomodulatory drugs have been used in patients with prominent systemic manifestations of SS as is done in patients with systemic lupus erythematosus. However, few randomized, double-blind, clinical trials have been carried out to establish whether these immunomodulatory agents are beneficial in SS.

Consideration should be given to the treatment of other problems associated with SS. For renal tubular acidosis, oral alkaline medications containing sodium and potassium citrate at a dose of 1–2 mEq/kg/day may be necessary to correct acidosis and decrease the risk of kidney stones. Also, urine calcium levels should be monitored. Renal tubular acidosis promotes mobilization of calcium from bone, which requires appropriate monitoring and treatment. Bronchodilators may benefit patients with a chronic cough, since SS is associated with increased airway reactivity. Thyroid disorders in SS patients are managed in the same manner as for other patients of similar age and sex. Dyspepsia and gastroesophageal reflux are not uncommon and require standard therapy. The arthritis occurring in SS patients responds well to the standard therapies used in rheumatoid arthritis. Dry skin may be alleviated by decreased frequency of bathing and application of lubricants. Pruritis may be treated with mentholated lotions. Superficial vasculitis and dermatitis are treated with steroids. Vaginal dryness and dyspareunia may respond to

water-soluble lubricants and vaginal estrogen preparations may be beneficial in postmenopausal females.

The understanding of SS continues to advance. However, only symptomatic therapies have been specifically approved for the treatment of this debilitating disorder and further investigation will be necessary to clarify the role of immunomodulatory agents. Replacement of destroyed salivary gland tissue by artificial salivary glands and the possibilities for gene therapies are under consideration as future treatment options.

## See Also the Following Articles

**Salivary Glands, Anatomy and Histology • Salivary Glands, Physiology • Xerostomia**

## Further Reading


Anaya, J. M., and Talal, N. (1999). Sjögren's syndrome comes of age [see comments]. *Semin. Arthritis Rheum.* 28, 355–359.

Atkinson, J. C., and Baum, B. J. (2001). Salivary enhancement: Current status and future therapies. *J. Dent. Educ.* 65, 1096–1101.

Atkinson, J. C., and Wu, A. J. (1994). Salivary gland dysfunction: Causes, symptoms, treatment. *J. Am. Dent. Assoc.* 125, 409–416.

Bell, M., Askari, A., Bookman, A., Frydrych, S., Lamont, J., McComb, J., Muscoplat, C., and Slomovic, A. (1999). Sjögren's syndrome: A critical review of clinical management [published erratum appears in *J. Rheumatol.* (1999) 26, 2718]. *J. Rheumatol.* 26, 2051–2061.

Bloch, K. J., Buchanan, W. W., Wohl, M. J., and Bunim, J. J. (1992). Sjögren's syndrome: A clinical, pathological, and serological study of sixty-two cases. *Medicine* 71, 386–401.

Drosos, A. A., Andonopoulos, A. P., Costopoulos, J. S., Papadimitriou, C. S., and Moutsopoulos, H. M. (1988). Prevalence of primary Sjögren's syndrome in an elderly population. *Br. J. Rheumatol.* 27, 123–127.

Fox, R. I., and Maruyama, T. (1997). Pathogenesis and treatment of Sjögren's syndrome. *Curr. Opin. Rheumatol.* 9, 393–399.

Fox, R. I., Tornwall, J., and Michelson, P. (1999). Current issues in the diagnosis and treatment of Sjögren's syndrome. *Curr. Opin. Rheumatol.* 11, 364–371.

Julkunen, H., Siren, M. K., Kaaja, R., Kurki, P., Friman, C., and Koskimies, S. (1995). Maternal HLA antigens and antibodies to SS-A/Ro and SS-B/La: Comparison with systemic lupus erythematosus and primary Sjögren's syndrome. *Br. J. Rheumatol.* 34, 901–907.

Pillemer, S. R., Matteson, E. L., Jacobsson, L. T., Martens, P. B., Melton, L. J., III, O'Fallon, W. M., and Fox, P. C. (2001). Incidence of physician-diagnosed primary Sjogren syndrome in residents of Olmsted County, Minnesota. *Mayo Clin. Proc.* 76, 593–599.

Pflugfelder, S. C., Solomon, A., and Stern, M. E. (2000). The diagnosis and management of dry eye: A twenty-five-year review. *Cornea* 19, 644–649.

Provost, T. T., and Watson, R. (1992). Cutaneous manifestations of Sjögren's syndrome. *Rheum. Dis. Clin. North Am.* 18, 609–616.

Sheikh, S. H., and Shaw-Stiffel, T. A. (1995). The gastrointestinal manifestations of Sjögren's syndrome. *Am. J. Gastroenterol.* 90, 9–14.

Strickland, R. W., Tesar, J. T., Berne, B. H., Hobbs, B. R., Lewis, D. M., and Welton, R. C. (1987). The frequency of sicca syndrome in an elderly female population. *J. Rheumatol.* 14, 766–771.

Tapinos, N. I., Polihronis, M., Tzioufas, A. G., and Moutsopoulos, H. M. (1999). Sjögren's syndrome: Autoimmune epithelitis. *Adv. Exp. Med. Biol.* 455, 127–134.

Thomas, E., Hay, E. M., Hajeer, A., and Silman, A. J. (1998). Sjögren's syndrome: A community-based study of prevalence and impact [see comments]. *Br. J. Rheumatol.* 37, 1069–1076.

Vitali, C., Bombardieri, S., Jonsson, R., Moutsopoulos, H. M., Alexander, E. L., Carsons, S. E., Daniels, T. E., Fox, P. C., Fox, R. I., Kassan, S. S., Pillemer, S. R., Talal, N., and Weisman, M. H. (2002). Classification criteria for Sjögren's syndrome. *Ann. Rheum. Dis.* 61, 554–558.

Voulgarelis, M., Dafni, U. G., Isenberg, D. A., and Moutsopoulos, H. M. (1999). Malignant lymphoma in primary Sjögren's syndrome: A multicenter, retrospective, clinical study by the European Concerted Action on Sjögren's Syndrome [see comments]. *Arthritis Rheum.* 42, 1765–1772.

# Small Bowel Transplantation

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**intestinal failure** An irreversible state of inability of the native gastrointestinal tract to provide for the nutritional and/or fluid and electrolyte demands of the body.

**isolated intestinal transplant** Vascularized transplantation of the jejuno-ileum from another person (usually a cadaver).

**liver–bowel transplant** Combined simultaneous transplantation of a liver and jejuno-ileum, requiring removal of the native liver.

**multivisceral transplant** Transplantation of the stomach, pancreas, and small intestine, and sometimes other organs, which may include the liver and/or kidney.

**parenteral nutrition** Administration of intravenous solutions (including carbohydrate, protein, fats, and water) sufficient to provide complete nutritional requirements.

**portal or mesenteric drainage** Venous effluent from a graft is directed into the superior mesenteric vein or portal vein, so that this blood undergoes a first-pass effect through the liver before entering the systemic circulation.

**systemic drainage** Venous effluent from a graft is directed to the systemic circulation via the vena cava, so that it does not first filter through the liver.

**Intestinal (small bowel) transplantation refers to the removal of the jejuno-ileum from one individual and the transplantation of this organ into another individual. This procedure requires reestablishment of mesenteric arterial inflow and mesenteric venous outflow from the graft and placement of the jejuno-ileal graft in the abdominal cavity. The jejuno-ileum can be transplanted alone, as an isolated small bowel graft, or in combination with a variety of other abdominal organs as part of composite or noncomposite grafts. Intestinal transplantation is generally performed for patients with intestinal failure (i.e., patients whose gastrointestinal tract functions too poorly to provide nutritional autonomy) or, less commonly, for patients with central abdominal tumors that cannot be removed without sacrificing the superior mesenteric vessels and small intestine.**

## BACKGROUND

Intestinal failure (the inability of the native gastrointestinal tract to provide nutritional autonomy) necessitates lifelong intravenous support to maintain caloric, fluid, or electrolyte homeostasis. Provision of replacement therapy in the form of parenteral nutrition, most often at home, permits survival for the majority of patients. Home parenteral nutrition is therefore the primary long-term therapy for patients with intestinal failure. For patients with intestinal failure, home parenteral nutrition can be considered analogous to renal replacement therapy for patients with end-stage kidney failure.

In some patients, however, the use of parenteral nutrition is limited by its complications, which include parenteral nutrition-associated liver disease, recurrent sepsis associated with line infections or bacterial overgrowth in the native intestinal tract, and loss of venous access for parenteral nutrition due to multiple-line-site thromboses. These complications and others contribute to death in 10–30% of patients with intestinal failure during the first 3–5 years on therapy. Patients with these complications are failing parenteral therapy and are therefore candidates for intestinal transplantation.

More than 50,000 North American patients currently receive parenteral nutrition for treatment of intestinal failure. It has been estimated that 15–20% of these patients are young and otherwise healthy and could be candidates for transplantation. It has also been estimated that 2 new live births per million in Western countries will eventually develop intestinal failure. Thus, although the current population receiving intestinal transplantation is small, with approximately 111 such operations having been performed in North America in 2001, there is a large population for whom this therapy could be useful when success is optimized.

## INDICATIONS

Indications for intestinal transplantation can be categorized as being related to loss of intestinal length (short bowel syndrome), loss of intestinal function, or tumors (Fig. 1).

Short bowel syndrome, in which intestinal length and absorptive surface area have been lost due to surgical resection, is the most common cause of intestinal failure leading to intestinal transplantation. The loss of

 

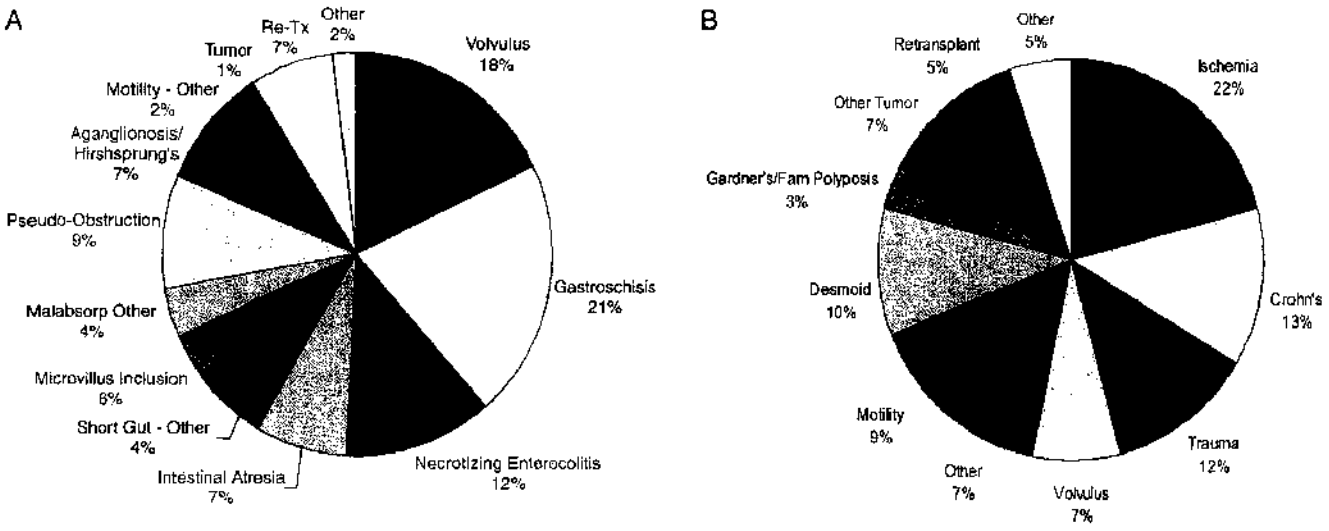


FIGURE 1 Pie charts illustrate the current indications for intestinal transplantation in children (A) and adults (B). Data from the Intestinal Transplant Registry. Available at http://www.intestinaltransplant.org. Accessed January 13, 2003.

mucosal absorptive surface area is associated with malabsorption and rapid transit time through the jejuno-ileum, with resultant malnutrition, recurrent dehydration, and electrolyte abnormalities. Short bowel syndrome may be secondary to a variety of diseases in adults and children, most of which are secondary to vascular or ischemic insults. In children, these include malrotation, volvulus, necrotizing enterocolitis, jejuno-ileal atresias, gastroschisis, omphalocele, and other congenital disorders. Adults frequently suffer short gut syndrome due to trauma, thrombosis or embolism to the mesenteric vessels, inflammatory bowel disease, volvulus, or other causes of infarction.

Functional disorders of the small intestine leading to intestinal failure include disorders of motility and disorders of enterocyte function. Motility disorders can be either myopathic or neuropathic. These include chronic idiopathic intestinal pseudo-obstruction, visceral myopathy, visceral neuropathy, total intestinal aganglionosis, and some forms of mitochondrial respiratory chain disorders that affect gastrointestinal motor function (e.g., mitochondrial neurogastrointestinal encephalomyopathy). Epithelial disorders that lead to secretory diarrhea or failure of absorption in the intestine are more common in children and include microvillus inclusion disease, tufting enteropathy, and autoimmune enteritis.

Tumors involving the base of the jejuno-ileal mesentery are often benign but are locally invasive and therefore lethal. Only complete resection of the tumor and sacrifice of the intestine can provide cure. The most common such lesions are desmoid tumors in patients with familial adenomatous polyposis. This tumor sometimes involves the mesenteric vessels, foreshortens the mesentery, and requires complete exenteration of the small bowel for complete resection. Sometimes these tumors involve other foregut organs that provide portal flow to the liver, such as the pancreas, spleen, stomach, and duodenum. Exenteration of these organs requires concurrent transplantation. Therefore, patients with desmoid tumors sometimes do not have intestinal failure and are not dependent on parenteral nutrition before resection and transplantation, which may be performed concurrently.

## TYPES OF TRANSPLANTS

Intestinal transplantation may be performed with an isolated intestinal graft or as a multiorgan transplant procedure. The common element of these procedures is transplantation of the jejuno-ileum, with or without other organs. Under current protocols, an ileostomy is created to allow for easy endoscopic surveillance of the graft for pathology in the early period after transplant. An enteric feeding tube is also placed to allow the early delivery of enteral nutrition, in case oral intake is not complete but the transplanted intestine can provide the full nutritional needs. This is not uncommon among babies who suffer neonatal short gut syndrome and were therefore never fed by mouth during infancy. Even if these children have a fully functional intestinal tract after transplant, they may still require enteral tube feeding while acquiring feeding skills. The different

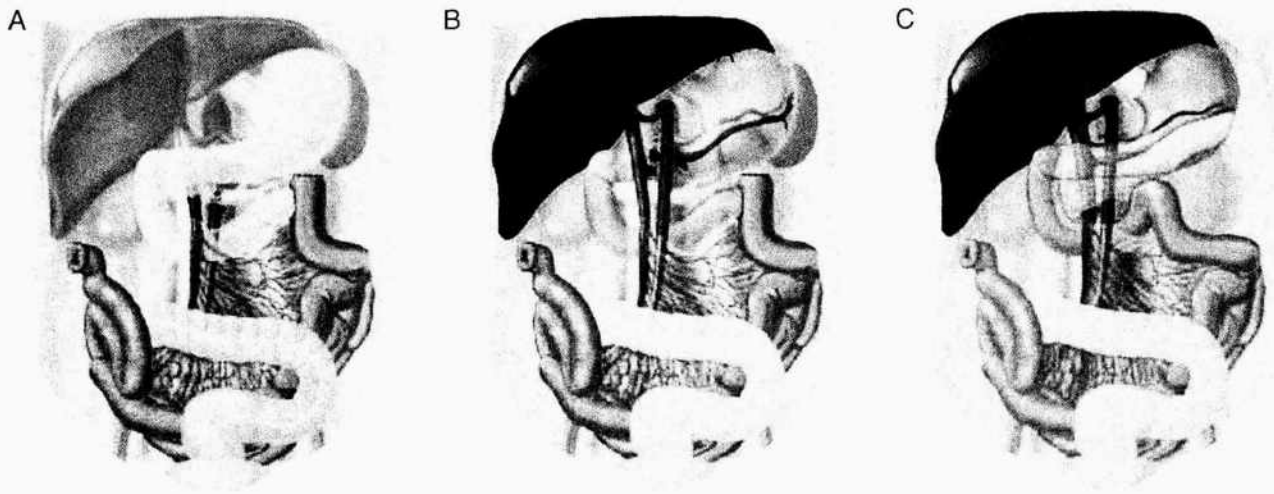


FIGURE 2 Illustrated are the three most common intestinal transplant procedures, which include (A) isolated intestine transplantation with mesenteric venous outflow; (B) liver–intestine transplantation with portacaval shunt draining the native foregut; and (C) multivisceral transplantation. Shaded areas represent native organs; dark areas represent transplanted organs. Reprinted, with permission, from Fishbein, T. M., Gondolesi, G. E., and Kaufman, S. S. (2003). Intestinal transplantation for gut failure (Review). *Gastroenterology*, 124, 1615–1628.

types of intestinal transplant procedures are illustrated in Fig. 2 and described below.

## Isolated Intestinal Transplantation

Isolated intestinal transplantation may be performed with mesenteric/portal drainage or systemic drainage. The drainage refers to the venous outflow of the grafted organ, which may be through the liver (mesenteric/portal) or into the inferior vena cava (systemic), utilizing a variety of surgical techniques. Gastrointestinal continuity is then reestablished, providing the recipient with the ability to take nutrition enterally. Isolated intestinal transplantation is generally indicated when there is intestinal failure without significant underlying liver disease or failure of other organs.

## Liver–Intestine Transplantation

Liver–intestine transplantation includes the jejunoileum and liver and generally involves transplantation of these organs with an intact mesenteric–portal circulatory system. Because the native foregut is preserved (native stomach, pancreas, duodenum, and spleen), a portocaval shunt must be performed to provide venous drainage of these organs when the composite liver–bowel graft is transplanted. These two organs may also be transplanted with or without the duodenum and intact biliary system. Transplantation of the organs with an intact duodenum and a portion of the head of the pancreas allows transplantation of the biliary system without disruption and is advantageous in small pediatric patients. This approach is referred to as liver–intestine transplantation with duodenal preservation. Alternatively, the liver and intestine may be transplanted without the duodenum, with a biliary anastomosis created between the donor common bile duct and the transplanted jejunum, with the mesenteric and portal venous system remaining intact. Finally, the patient may receive an orthotopic liver transplant and an isolated intestine transplant, in which the two organs are both transplanted, but not as a composite graft. Combined liver and intestinal transplantation is generally indicated when intestinal failure is accompanied by liver failure, usually due to parenteral nutrition.

## Multivisceral Transplantation

Multivisceral transplantation involves transplantation of the stomach, pancreas, and small intestine and sometimes also the liver and/or the kidney. These transplants are always performed as composite organ allografts and involve placement of the new gastrointestinal tract in the native position in the abdomen. Exenteration of the native organs, including the stomach, pancreas, duodenum, spleen, and small bowel, is therefore required. The right colon, receiving its blood supply from the superior mesenteric artery, also must be resected. Since removal of the donor organs necessitates vagal

nerve transection, the pylorus lacks a native vagal relaxation reflex and pyloroplasty is required.

### Donor Organ Selection and Procurement

In most cases, donor organ procurement requires a blood-group-identical or -compatible, hemodynamically stable cadaver donor. For isolated intestinal transplantation, the entire jejuno-ileum is usually procured with the superior mesenteric artery and vein and the pancreas and liver may be procured for transplantation elsewhere. When a composite liver and small bowel graft is procured, the shared mesenteric–portal venous drainage of the two organs precludes separate transplantation of the pancreas alone. For multivisceral transplantation, the stomach, pancreas, spleen, small bowel, and liver are procured *en bloc* and the spleen can then be removed in a chilled ice bath. Because the small bowel is a hollow viscus, it is particularly prone to warming and preservation injury, and core cooling with a standard preservation solution (University of Wisconsin solution, Viaspan) is the central tenet of organ preservation. Ischemic time must be kept short and every attempt is made to reperfuse the organ within 12 h after its removal from the donor circulation. Whereas most intestinal transplants have been performed with cadaveric donor organs as described here, only a few transplants have used live-donor partial ileal or jejunal grafts with mixed results. Live donor transplantation is ideal when the patient has an identical twin donor and immunosuppression is therefore not required. Finally, newer reduced-size techniques are being developed to address the shortage of grafts for small children.

## MANAGEMENT AFTER TRANSPLANTATION

Management after transplantation requires intensive immunosuppressive therapy to prevent allograft rejection, early recognition of rejection when it occurs, prophylaxis against and recognition and treatment of infectious disorders, and nutritional management.

### Surveillance Endoscopy

Surveillance endoscopy is the standard method for diagnosing rejection after transplantation. Currently, there is no noninvasive means to reliably predict or detect rejection of the transplanted jejuno-ileum. Therefore, protocol biopsies are performed at variable intervals, usually weekly or twice weekly, early after transplantation. Rejection cannot be diagnosed solely on the basis of the gross endoscopic appearance of the intestinal mucosa. The process has been shown to be patchy, with areas of normal mucosa interspersed with areas that demonstrate rejection. Therefore, multiple random mucosal pinch biopsies are generally sampled for histologic review.

### Review

Rejection is common after intestinal transplantation, with the process directed at the crypt epithelium. Enterocyte apoptosis in the crypt is generally present with rejection early after transplantation (mild rejection), variably associated with an increase in the density of the lamina propria infiltrate, activated lymphocytes, acute cryptitis, and variable degrees of villous blunting (moderate rejection). Such changes are usually, but not always, associated with secretory diarrhea, the clinical hallmark of most posttransplant pathologies. Accompanying changes may include development of mucosal congestion, fever, leukocytosis and sometimes development of ileus. These changes, if not adequately treated, lead to the dissolution of crypts and eventual loss of mucosal architecture, leading to sloughing of the epithelium from the underlying submucosa (severe rejection). Anti-lymphocyte antibody preparations are often required to treat advanced rejection.

### Immunosuppression

The gastrointestinal tract harbors approximately 80% of the body's total lymphoid tissue. Due in part to this heightened immunogenicity over other solid organs, the small intestine has been a troublesome organ to transplant. Rejection is more common and more commonly severe than with other solid organ transplants. Immunosuppression after intestinal transplantation is currently based on calcineurin blockade, with other agents variably used in different protocols. Corticosteroid use generally accompanies the calcineurin inhibitor, with global immunosuppression exceeding that required for successful transplantation of the kidney or liver. Prior to the use of tacrolimus in intestinal transplantation, graft survival was poor and marred by high rates of death resulting from rejection and concomitant infections. Recently, various approaches, including the use of monoclonal interleukin-2 antagonists, graft irradiation, and concomitant use of rapamycin, all in combination with tacrolimus, appear to have decreased the rates of acute cellular rejection compared to historical controls. When acute cellular rejection occurs, augmentation of immunosuppression is required. Mild rejection often responds to bolus administration of intravenous corticosteroids,

whereas moderate or severe rejection usually requires administration of depleting anti-lymphocyte antibodies.

### Infection Prophylaxis

Prior to procurement, most programs attempt to decontaminate the intestinal allograft of bacterial and fungal organisms by administering enteric antibiotics to the donor. Decontamination using mechanical cleansing is impractical in cadaver donors. Intravenous antibiotics are usually given to the recipient during transplantation, as the donor organ is not sterile. Furthermore, because the level of immunosuppression necessary for successful prophylaxis of rejection puts recipients at risk for viral infection, prophylaxis with hyperimmune globulin and antiviral agents (usually ganciclovir) is generally employed against the most common pathogens (e.g., cytomegalovirus and Epstein-Barr virus). However, newer viral pathogens, including adenovirus and calicivirus, have recently been described after intestinal transplantation.

## COMPLICATIONS

Intestinal transplantation is a complex undertaking. The complications seen after this transplant can be categorized as surgical, infectious, or immunological.

### Surgical Complications

Because the transplanted intestine has undergone ischemic and reperfusion injuries, some degree of mucosal injury is usually present early after transplantation. Mucosal injury can contribute to poor healing, anastomotic leakage, and loss of barrier function, leading to translocation and peritonitis and, often, to the need for early reoperation. Complex vascular reconstructions are required for this transplant, predisposing to postoperative bleeding. Transection of the mesentery and lymphatic drainage of the intestine may result in the development of chylous ascites after transplant. Chylous or lymphatic ascites may arise from the donor organ or from lymphatics of the native intestine in cases where enterectomy is required at the time of transplantation. Chylous ascites usually presents once a fat-containing enteral diet is begun and it resolves within 6 weeks with administration of a diet low in long-chain triglycerides.

### Infectious Complications

Line-related sepsis can occur after transplantation, during the interval before weaning from parenteral therapy. Bacterial and fungal infections that are common before transplant in patients on parenteral therapy may recur with immunosuppression after intestinal transplantation. Peritonitis early after transplant is common, due either to contamination of the field during the transplant procedure or to translocation. Peritonitis usually does not respond to antibiotic therapy and requires reoperation with peritoneal lavage. Later, during the first year after transplantation, viral infections are common; these usually infect the host organ. Cytomegalovirus infection can cause a secretory diarrhea, as can adenovirus infection of the graft. Both viruses may also disseminate, causing a viral syndrome or, less commonly, lethal sepsis. Distinguishing these opportunistic viral infections from rejection can be difficult, as crypt inflammation and diarrhea are the clinical hallmarks of both. Epstein-Barr virus-related B-lymphocyte proliferations also occur after transplantation and have been reported in up to 20% of recipients in some series. This complication, particularly common among naive pediatric transplant recipients, frequently affects the transplanted intestine. It can be seen as expanded lymphoid nodules with activated or atypical lymphocytes on mucosal pinch biopsies of the graft. If untreated, these can progress to lethal monoclonal proliferations. Polymerase chain reaction serum evaluation aids in the early diagnosis and treatment of these viruses.

### Rejection

In most clinical reports, more than 80–90% of patients experience at least one episode of acute cellular rejection during the first year after transplantation. Enterocyte apoptosis in the crypt is generally present with rejection early after transplantation (mild rejection) and can be associated with an increase in the density of the lamina propria infiltrate, activated lymphocytes, acute cryptitis, and variable degrees of villous blunting (moderate rejection). If detected early, these changes are usually reversible with bolus steroid administration. If not recognized and treated, however, they may progress to dissolution of crypts, loss of mucosal architecture, and separation of the epithelium from the underlying submucosa (severe rejection). Anti-lymphocyte antibody preparations are required to treat advanced rejection and the process is often not reversible when it has reached this stage.

The rejection process, and the resultant mucosal injury, leads to loss of intestinal epithelial barrier function and is frequently associated with translocation of bacteria and systemic sepsis or peritonitis. Sloughing of the mucosal lining may occur, with bleeding and malabsorption. This combination of events, requiring intensive augmentation of immunosuppression in the face of accompanying infection, accounts for the high

mortality rate associated with intestinal transplantation. If the recipient has received an isolated intestinal allograft, the organ may be sacrificed and removed. Such patients may later undergo successful retransplantation. Referral of patients with sufficient venous access and liver reserve to allow an interval of parenteral therapy is critical to provide this alternative. When the transplanted intestine is part of a multiorgan graft, removal of the donor organs is not feasible. Thus, transplantation of a multiorgan intestinal allograft is an irreversible step, leading either to resolution and repair of the damaged graft or to the ultimate demise of the patient. Despite considerable historical rodent data to support the protective effect of the liver against development of intestinal rejection, the ability to remove the isolated intestinal allograft in part accounts for the improved overall patient survival seen with isolated intestinal transplants in humans.

Chronic rejection, leading to arteriolitis of the graft vasculature, fibrosis of the muscular layers of the small bowel, chronic distortion of the mucosal villous architecture, and allograft dysfunction with altered motility and malabsorption, has also been reported. The clinical diagnosis remains enigmatic, but is usually associated with recurrent diarrhea, worsening nutrition, and motility disturbances.

Recently, various approaches in different centers appear to have decreased the rates of acute cellular rejection compared to historical controls. A number of new agents may have an effect on intestinal allograft survival. Humanized interleukin-2 inhibitors, which have been introduced and studied in other solid organ transplant populations, inhibit the ability of the activated T lymphocyte to up-regulate the immune response through recruitment of other such cells. Sirolimus use in combination with tacrolimus has also significantly decreased the rate of acute cellular rejection and increased the rates of graft survival. Although no randomized studies have evaluated these agents in intestinal transplantation because of the small number of patients involved, experience at several centers indicates a reduction in early rejection rates from nearly 90% historically to under 20% in some series.

Other approaches have included attempts to augment chimerism and improve graft survival rates through the infusion of unmodified donor bone marrow cells. Early reports from Pittsburgh failed to confirm decreased rejection rates among patients treated in this manner. The augmentation of chimerism through infusion of stem cells remains to be studied, however, and may prove more effective. More recently, researchers have attempted to inactivate donor antigen-presenting cells by irradiating donor intestinal allografts prior to implantation.

## RESULTS

Success with intestinal transplantation has lagged behind that of other solid organ transplants, owing both to the various factors detailed above and to the advanced state of chronic illness seen in most patients referred for transplantation. The International Intestinal Transplant Registry on Recipient Outcomes last published its results in 1999 and reported a 69% 1-year survival rate for both patient and graft in isolated intestine transplants and 66% patient and 63% graft survival rates at 1 year for liver/bowel and multivisceral transplants. More recently, unpublished registry data demonstrate improved survival for all graft types and better survival at more experienced centers among patients who did not require hospitalization immediately prior to transplantation and among those receiving isolated intestine grafts. Whereas initial reports indicated that pediatric patients had higher rates of survival, more recently no significant survival advantage appears to occur in pediatric recipients.

Overall, series including transplants performed in the early 1990s report low survival rates for all recipients, with 1- and 3-year survival rates of 63 and 55% in one series of 17 patients from the UCLA Medical Center. Recent single-center series have reported higher patient and graft survival rates, including 1-year patient survival rates of up to 89% among isolated intestinal allograft recipients in one report from University of Nebraska and pediatric liver and bowel recipient survival rates of approximately 70% at 2 years in another report from Pittsburgh. Another study reported 1- and 5-year survival rates of 75 and 54% among 155 patients. Another report on 95 transplants from the University of Miami demonstrated 1-year patient and graft survival rates of 84 and 72%, respectively, among recipients of isolated intestine transplants performed since 1998, compared to 1-year liver–survival rates of only 40 and 48%, respectively, in bowel and multivisceral transplant patients. Thus, it appears that overall patient and graft survival rates are improving. Several factors have contributed to improved survival rates in intestinal transplantation. Immunosuppressive management including the use of newer agents has led to decreases in the rate of acute cellular rejection. In one report from The Mount Sinai Medical Center, this correlated with a significant improvement in graft survival rates. Additionally, earlier and more accurate diagnosis and management of viral infectious complications appear to have decreased the mortality rate associated with these diseases.

The majority of survivors (more than 70%) have full graft function with no requirement for parenteral therapy, although most recipients of intestinal

transplants require some antidiarrheal medications. Although linear growth may be attained in the majority of surviving children after successful transplantation, catch-up growth is not necessarily achieved. The majority of indications for intestinal transplantation include congenital anomalies or vascular accidents, leading to surgical resection, and therefore recurrence of the underlying disease is not common. Only one patient with Crohn's disease is known to have suffered recurrence of this disease leading to failure of the allograft.

## See Also the Following Articles

**Liver Transplantation • Parenteral Nutrition • Short Bowel Syndrome • Transplantation Immunology**

## Further Reading

Carbonnel, F., Cosnes, J., Chevret, S., Beaugerie, L., Ngo, Y., Malafosse, M., Parc, R., Le Quintrec, Y., and Gendre, J. P. (1996). The role of anatomic factors in nutritional autonomy after extensive small bowel resection. *J. Paren. Enteral. Nutr.* 20, 275–280.

Fishbein, T. M., Gondolesi, G. E., and Kaufman, S. S. (2003). Intestinal transplantation for gut failure (Review). *Gastroenterology* 124, 1615–1628.

Fishbein, T. M., Schiano, T., LeLeiko, N., Facciuto, M., Ben-Haim, M., Emre, S., Sheiner, P. A., Schwartz, M. E., and Miller, C. M. (2002). An integrated approach to intestinal failure: Results of a new program with TPN, bowel rehabilitation and transplantation. *J. Gastrointest. Surg.* 6, 554–562.

Grant, D. (1996). Current results of intestinal transplantation. The International Intestinal Transplant Registry. *Lancet* 347, 1801–1803.

Intestinal Transplant Registry. Available at http://www.intestinal-transplant.org. Accessed January 13, 2003.

Kaufman, S., Atkinson, J., Bianchi, A., Goulet, O., Grant, D., Langnas, A., *et al.* (2001). Indications for pediatric intestinal transplantation: A position paper of the American Society of Transplantation. *Pediatr. Transplant* 5, 80–87.

Khan, F. A., and Tzakis, A. G. (1999). Intestinal and multivisceral transplantation. *In* "Transplantation" (L. C. Ginns, A. B. Cosimi, and P. J. Morris, eds.), p. 422. Blackwell Science, Malden, MA.

Messing, B., Crenn, P., Beau, P., *et al.* (1999). Long-term survival and parenteral nutrition dependence in adult patients with short bowel syndrome. *Gastroenterology* 117, 1043–1050.

Nightingale, J. M. D. (ed.) (2001). "Intestinal Failure." Greenwich Medical Media Ltd., London, UK.

Starzl, T. E., Todo, S., Tzakis, A., *et al.* (1991). The many faces of multivisceral transplantation. *Surg. Gynecol. Obstet.* 172, 335–344.

Todo, S., and Tzakis, A. G. (1996). Transplantation of the liver with digestive organs. *In* "Transplantation of the Liver" (R. W. Busuttil and G. B. Klintmalm, eds.), p. 503. W. B. Saunders, Philadelphia, PA.

Todo, S., Tzakis, A. G., Abu-Elmagd, K., *et al.* (1992). Intestinal transplantation in composite visceral grafts or alone. *Ann. Surg.* 216, 223–234.

Wilmore, D. W., Lacey, J. M., Soultanakis, R. P., Bosch, R. L., and Byrne, T. A. (1997). Factors predicting a successful outcome after pharmacologic bowel compensation. *Ann. Surg.* 226, 288–293.

# Small Intestinal Motility

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**migrating motor complex** Specific pattern of small intestinal motility that begins when digestion of a meal is complete and ends with intake of the next meal; also called interdigestive motility.
**motilin** Hormone released by enteroendocrine cells in the gut.
**physiologic ileus** Normal absence of gastrointestinal contractile activity.
**power propulsion** Specific pattern of motility that rapidly propels luminal contents over extended distances in the small and large intestine.
**segmentation** Specific pattern of small intestinal motility that starts with the ingestion of a meal and accomplishes mixing of the contents in the lumen; also called digestive motility.
**vagotomy** Surgical sectioning of the vagus nerves.

**Transit time for meals moving from stomach, to small intestine, to large intestine is measured in hours. In these three compartments, transit occurs most rapidly as ingested food passes through the stomach; the slowest transit time occurs in the large intestine. Three fundamental patterns of motility that influence transit of material through the small intestine are the interdigestive pattern, the digestive pattern, and power propulsion. Each pattern is programmed by the enteric nervous system.**

## INTERDIGESTIVE MOTILITY PATTERN

The interdigestive pattern of small intestinal motility, called the migrating motor complex (MMC), begins after digestion and absorption of nutrients are complete, about 2–3 hours after a meal. The contractile behavior is detected by placing pressure sensors in the lumen of the intestine or by attaching electrodes to the intestinal surface. Sensors in the stomach show the MMC starting as large-amplitude contractions in the distal stomach. The MMC in the stomach migrates into the duodenum and on through the small intestine to the ileum. As it ends in the terminal ileum, the next cycle starts in the stomach.

At a single recording site in the intestine, the MMC pattern consists of three consecutive phases: (1) a silent period, Phase I, which involves no contractile activity and corresponds to physiologic ileus, (2) phase II, which consists of irregularly occurring contractions, and (3) phase III, which consists of regularly occurring contractions. Phase I returns after Phase III ends and the cycle is repeated after 80–120 minutes in humans. With multiple sensors positioned along the intestine, slow propagation of the Phase II and Phase III activity down the intestine becomes evident.

At any given time, the MMC occupies a limited length of intestine called the "activity front," which has an upper and a lower boundary. The activity front slowly advances (migrates) along the intestine at a rate that progressively slows as the front approaches the ileum. Peristaltic propulsion of luminal contents in the aboral direction occurs between the oral and aboral boundaries of the activity front. The waves of peristalsis start at the oral boundary and propagate to the aboral boundary of the activity front. Successive peristaltic waves start on average slightly further in the aboral direction and propagate on average slightly beyond the boundary where the previous wave stopped. Thus, the entire activity front slowly migrates down the intestine, sweeping the lumen clean as it goes.

Cycling of the MMC continues until it is ended by the ingestion of more food. A sufficient nutrient load terminates the MMC simultaneously at all levels of the intestine. Termination requires the physical presence of a meal in the upper digestive tract. The speed with which the MMC is terminated at all levels of the intestine suggests a neural or hormonal mechanism. Gastrin and cholecystokinin, both of which are released during a meal, terminate the MMC in the stomach and upper small intestine when injected intravenously.

The MMC is organized by the enteric nervous system. It continues in the small intestine after interruption of neural input from the central nervous system, but stops when it reaches a region of the intestine where the enteric nervous system has been damaged. Presumably, command signals to the enteric neural circuits are necessary for initiation of the interdigestive pattern; nevertheless, whether the commands are neural or hormonal or both is unknown. Although levels of the hormone motilin increase in the blood at the onset of

 

the interdigestive state, it is unclear whether motilin triggers the MMC or is released as a consequence of it.

## DIGESTIVE MOTILITY PATTERN

Mixing movements in the small intestine characterize the digestive state. Feeding interrupts the interdigestive pattern and converts small intestinal motor behavior to a fed pattern characteristic of the digestive state. The fed pattern is distinguished by peristaltic contractions that propagate for only very short distances. This activity occurs continuously along the length of the intestine. Because each short segmental contraction does not propagate far, it jets the chyme in both directions. These contractions, spaced closely together as they are along the bowel, accomplish mixing of the luminal contents and, over time, net aboral propulsion of the luminal contents.

Commands transmitted from the brain by the vagus nerves sustain the digestive motility pattern in the small intestine. Transmitted vagal command signals are important in the conversion from the fasting to the fed pattern. After vagotomy, a larger quantity of ingested food is necessary for interruption of the interdigestive motor pattern, and interruption of the migrating motor complex is often incomplete. During the fed pattern, blockade of impulse transmission in the vagus nerves results in interruption of the digestive pattern.

## POWER PROPULSION

Power propulsion is a defensive response to the presence of harmful agents in the intestinal lumen. Power propulsion involves strong, long-lasting contractions of the circular muscle. These "giant" migrating contractions, which propagate for extended distances along the intestine, are considerably stronger than the peristaltic contractions seen during the migrating motor complex or in the digestive motility pattern. Giant migrating contractions last 18–20 seconds. They reflect a highly efficient propulsive mechanism that rapidly strips the lumen clean as they travel over long lengths of intestine, at a rate of about 1 cm/sec. Small intestinal power propulsion differs from peristaltic propulsion during the migrating motor complex and from the mixing movements of the digestive motility pattern in that circular contractions in the propulsive segment are much stronger and they propagate over much longer reaches of intestine.

Power propulsion occurs in the oral direction during emesis and in the anal direction in response to noxious stimulation in the small intestine. The power propulsion pattern starts in the midjejunum and propagates to the stomach during emesis. When initiated by noxious stimulation, propulsion may start in the midregions of the small intestine and travel all the way to the ileocecal junction. Abdominal cramping sensations and diarrhea are associated with this motility pattern. Application of irritants to the mucosa, the introduction of luminal parasites, enterotoxins from pathogenic bacteria, allergic reactions, and exposure to ionizing radiation all trigger the power propulsion pattern of motility. This suggests that power propulsion is a defensive adaptation for rapid clearance of undesirable contents from the intestinal lumen. Propulsion clears the upper bowel as part of the emetic response and clears the lower small intestine by rapid movement of the material into the colon.

### See Also the Following Articles

**Emesis • Enteric Nervous System • Migrating Motor Complex • Motilin • Physiologic Ileus • Postprandial Motility • Power Propulsion (590) • Small Intestine, Absorption and Secretion**

### Further Reading

Wood, J. (1994). Physiology of the enteric nervous system. *In* "Physiology of the Gastrointestinal Tract" (L. Johnson, D. Alpers, J. Christensen, E. Jacobson, and J. Walsh, eds.), 3rd Ed., Vol. 1, pp. 423–482. Raven Press, New York.

Wood, J. (2003). Neurogastroenterology and digestive motility. *In* "Medical Physiology" (R. Rhoades and G. Tanner, eds.). 2nd Ed., pp. 449–480. Chap. 26. Lippincott Williams & Wilkins, Baltimore.

Wood, J., and Castel, D. (2000). "Neurogastroenterology and Motility: Upper Gastrointestinal Tract." Milner-Fenwick, Timonium, Maryland.

# Small Intestine, Absorption and Secretion

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**apical membrane** Portion of the intestinal epithelial cell plasma membrane facing the intestinal lumen (the exterior of the body).

**basolateral membrane** Portion of the intestinal epithelial cell plasma membrane facing the blood (interior of the body).

**chyme** Slurry of partially digested foods and liquids that is transiently present in the intestines following a meal.

**diarrhea** Frequent passage of watery stool.

**electrolytes** Charged ions, such as sodium and chloride, that are part of the ionic composition of body fluids.

**epithelial polarity** The property of epithelial cell asymmetry. Epithelial cells sit at the interface between two compartments and the cells have different surface and cellular features along an imaginary axis drawn between the two compartments.

**osmolyte** A molecule that can be dissolved in a solvent (most commonly water) and thereby contribute to the total concentration of particles in the solvent, adding to the osmolarity.

**paracellular transport** Vectorial transport of material through the extracellular spaces between adjacent epithelial cells. Results in net movement of material between the two compartments faced by epithelial cells.

**transcellular transport** Vectorial transport of material through the cytosol of epithelial cells. Results in net movement of material between the two compartments faced by epithelial cells.

**transepithelial transport** Vectorial transport of material across the epithelial layer, using either paracellular or transcellular routes.

**The major function of the small intestine is to efficiently absorb a wide variety of nutrients and electrolytes from ingested foods. As a consequence of these absorptive processes, water is also absorbed and the lumenal contents become drier. To keep the intestinal chyme well hydrated (to promote easier mixing, intestinal transit, and solubility of remaining nutrients), the small intestine also secretes fluid into the lumen. For this reason, both absorptive and secretory processes occur simultaneously. During normal intestinal function, fluid absorption exceeds secretion so that virtually all of the lumenal fluid will ultimately be absorbed by the concerted action of both the small and large intestines. This is important to supply water as well as nutrients and electrolytes to the body. However, in diarrheal diseases, secretory activity exceeds absorption. In this case, water is lost to the stool and life-threatening dehydration can result. The intestinal epithelium mediates all vectorial transport of substances between the body and the intestinal lumen. This single layer of epithelial cells sits at the interface between these two compartments and simultaneously acts as a selective barrier to undesirable lumenal contents and as a portal to needed lumenal contents. Each individual epithelial cell has a polarized architecture, with distinct surface features present in the membrane facing the gut lumen (apical membrane) versus the membrane facing the blood (basolateral membrane). It is the specialized properties of the intestinal epithelial cell membranes that underlie the ability to perform the net transport of substances between the body and the gut lumen. The body dynamically regulates the function of proteins that mediate these properties and thereby regulates the processes. It should be recognized that epithelial absorptive functions vary along the length of the small intestine from the duodenum through the ileum, reflecting the need to absorb specific constituents from the lumen at specific locations.**

## INTRODUCTION

Ingested food must provide the body with necessary salts, nutrients, fluid, and osmolytes to sustain life. Assimilating these molecules must occur with a high level of specificity to avoid absorption of toxins, bacteria, and other undesired substances from the gut lumen. It must also occur in response to a meal that can require activation of these absorptive processes at any time of day or night and in response to a staggeringly diverse set of foodstuffs.

To cope with the massive amount of absorption that is required to sustain the body, the intestine has evolved multiple strategies to increase the surface area for absorption. The small intestine is not a smooth cylindrical tube, but rather has macroscopic folds that provide both enhanced surface area and extra space for distension following entry of chyme. On a smaller scale, fingerlike projections of tissue extend into the lumen several hundred micrometers, with the epithelial cells that mediate

 

absorption lining these intestinal villi. At a microscopic level, the apical membrane of each epithelial cell has abundant specialized membrane structures, termed microvilli, that are 2 to 5 μm long finger-like projections of the cell membrane into the lumen. Combined, these strategies increase the absorptive surface area approximately 600-fold compared to a smooth cylindrical tube of the same macroscopic dimensions.

The small intestine is responsible for absorption of the majority of salts, amino acids, carbohydrates, vitamins, and fats. In most cases, these absorptive processes occur due to the presence of membrane proteins that reside in the plasma membranes of intestinal epithelial cells and specifically bind and transport desired nutrients into the body. There are many such membrane transport proteins residing in the membrane and these products of multiple genes are each selective for one or a small group of substrates whose transport they facilitate. For example, the SGLT1 protein resides in the apical membrane and is responsible for the majority of glucose and galactose absorption. The GLUT5 protein resides in the same membrane, but is responsible for fructose absorption. Dividing the task of absorption among numerous proteins provides a mechanism for regulating the uptake of individual constituents of a meal (through regulation of the relevant transporters) and ensures that a high level of specificity for desirable versus undesirable constituents is sustained.

The small intestine absorbs both water-soluble and water-insoluble compounds. If absorbed molecules are dissolved in the aqueous lumenal fluid, then they act as osmolytes. Therefore, their absorption has the consequence of simultaneously stimulating absorption of water molecules, because of local differences in osmotic pressure between compartments (e.g., between the lumen and the epithelial cell cytosol). It is believed that water transport may be enhanced by the action of aquaporin water channels, specifically AQP8 and AQP4 proteins isoforms. In this manner, the absorption of solutes promotes the absorption of water and thereby tends to dehydrate the lumenal chyme. In contrast, the absorption of water-insoluble fats occurs because these compounds are emulsified by bile salts, compounds that act as solubilizers of fats because of their detergent properties.

Maintaining hydration of the lumenal chyme is essential to promote efficient absorption, a function that requires a well-mixed aqueous environment. To this end, the small intestine also secretes fluid. The secretory process present in all portions of the small intestine is chloride secretion, which promotes an attendant water secretion into the lumen. In addition to hydration of the lumen, the secretion of bicarbonate contributes to the maintenance of optimal pH values in the small intestinal lumen and the secretion of bioactive peptides promotes defense from bacterial pathogens. Coordinated contractions of the intestinal wall are needed to both mix the lumenal contents and propel them down the intestinal tract.

## THE INTESTINAL EPITHELIUM

The intestinal epithelium is a single layer of cells that form a lining to separate the intestinal lumen from the body. The lining acts in part as a general barrier to keep the body separate from the outside world represented by the lumen, with specialized junctional structures to fuse neighboring epithelial cells to each other and seal the epithelial layer. Epithelial transport acts to complement this function by providing routes for specific substances to enter (or leave) the body via their transepithelial transport between the lumen and the blood across the epithelial layer. The relevant transport routes are either through the epithelial cells (transcellular transport) or between the epithelial cells for those substances that have a limited permeability through the junctions (paracellular transport). In either case, absorbed substances are delivered directly to the basal side of the epithelial layer where diffusion of water-soluble substances into the portal blood, or diffusion of lipid-soluble materials into the lymphatic lacteals, allows the rapid transit of absorbed materials from the intestinal tissue to other parts of the body.

Transcellular transport requires the sequential flux of a substance across the apical and basolateral membranes. At each step, the involvement of an integral membrane protein is required. There are four classes of these membrane transporters. ATPases drive a substance across the membrane by transducing the energy from the cleavage of ATP. These are called primary active transporters because they are responsible for creating ion gradients that can act as a source of energy for other transporters. Ion-gradient-dependent transporters transduce this ion gradient energy into the transmembrane movement of other ions or solutes and are termed secondary active transporters. Facilitated diffusion transporters bind solutes or ions that are not carried by the ATPases and facilitate their equilibration across the membrane. Channels also dissipate gradients across the membrane, but act more as gated ion pores in the membrane. Transport across the apical membrane is the rate-limiting step for transcellular transport of most substances and is therefore a key site for the regulation of transport rates.

Tight junctions provide the rate-limiting step for paracellular transport. After passing this restrictive

site, fluid and solutes progress through the torturous extracellular spaces between adjacent epithelial cells.

The intestinal epithelium contains a diverse set of cells, some of which mediate absorptive and secretory processes. It is generally agreed that cells on the villus are absorptive and cells in the crypts are secretory. It remains unclear how and where the transition in function occurs along this "vertical axis" and whether crypt cells might also absorb some substances.

## ABSORPTION OF WATER-SOLUBLE MOLECULES

The small intestine has a large capacity to absorb water-soluble nutrients. In a normal Western diet, 40–70 g of protein is ingested per day, and even in the presence of an additional 50 g of secreted protein (mostly from the pancreas), 100% of this load is absorbed from the lumen of the small intestine. Similarly, 400 g of ingested carbohydrate is fully absorbed per day. In the latter case, it is known that the maximum capacity for carbohydrate absorption is approximately 1 kg/day. The ability of the intestine to absorb with such high efficiency is dependent on the mechanisms that have evolved to efficiently scavenge lumenal nutrients.

The small intestine uses a common strategy for absorption of many water-soluble molecules. Many lumenal nutrients are presented as polymers that must be digested by lumenal enzymes (either attached to the apical surface of epithelial cells or secreted into the gut lumen) prior to absorption of their simpler constituents. This strategy reduces the number of different molecules that must be recognized by transport proteins as absorbable nutrients. Transcellular transport is then initiated by apical uptake of the simpler constituents via either an ion-gradient-dependent or a facilitated diffusion transporter. Vitamins are absorbed in the original ingested form, since modifying these essential factors prior to absorption would not help the body. The absorbed nutrients within enterocytes then complete their transcellular route by leaving the cell through facilitated diffusion across the basolateral membrane.

Many molecules are absorbed by ion-gradient-dependent transporters in the apical membrane. Most of these transporters use the sodium electrochemical gradient (established by the basolateral $Na^+,K^+$-ATPase) as the energy source to drive apical cotransport of sodium and a nutrient (sugars, amino acids, vitamins, bile salts) into the enterocyte. The advantage of such cotransporters is that they can cause a high level of intracellular accumulation of the nutrient, leading to efficient absorption even with low lumenal levels of the nutrient. Examples of apical transporters for major dietary nutrients are shown in Table I, followed by a listing of facilitated diffusion carriers that are also present in the apical membrane.

**TABLE I Apical Membrane Absorptive Processes and Proteins**

| Driving ion | Solute class | Substrate specificity | Gene: Common symbol (NCBI symbol)[a] |
|---|---|---|---|
| Sodium | Sugars | Glucose, galactose | SGLT1 (SLC5A1) |
| Sodium | Amino acids | Neutral | ASCT1 (SLC1A4) |
| | | Anionic | EAAT3 (SLC1A1) |
| | | Imino | Uncloned |
| Sodium | Water-soluble vitamins | Ascorbate | SVCT1 (SLC23A2) |
| | | Biotin, pantothenate | SMVT (SLC5A6) |
| Sodium | Bile salts | Bile acids, bile salts | IBAT (SLC10A2) |
| Proton | Peptides | Dipeptides, tripeptides | PEPT1 (SLC15A1) |
| — | Sugars | Fructose | GLUT5 (SLC2A5) |
| — | Amino acids | Cationic | CAT1 (SLC7A2) |
| | | | 4F2HC (SLC7A7) |
| | | Neutral | RBAT + ATB0 (SLC3A1+SLC7A9?) |
| — | Water-soluble vitamins | Folate | FOLT1 (SLC19A1) |
| | | Thiamine | THTR1 (SLC19A2) |
| | | Nicotinamide (niacin) | Uncloned |
| | | Pyridoxamine ($B_6$) | Uncloned |
| | Salts | $Na^+/H^+$ exchange | NHE3 (SLC9A3) |
| | | | NHE2 (SLC9A2) |
| | | $Cl^-/HCO_3^-$ exchange | DRA (SLC26A3) |

[a] NCBI, National Center for Biotechnology Information.

Table 1 also lists the relevant carriers that absorb the majority of NaCl in the absence of other lumenal nutrients. In this mechanism, apical $Na^+/H^+$ exchange mediates sodium uptake into the enterocyte. The concomitant alkalinization of the cell causes activation of $Cl^-/HCO_3^-$ exchange in the same membrane, which mediates chloride uptake. Basolateral $Na^+,K^+$-ATPase promotes $Na^+$ efflux from the cell, completing the transcellular transit of $Na^+$. A basolateral $K^+/Cl^-$ cotransporter (KCC1, SLC12A4) mediates $K^+$ and $Cl^-$ efflux and completes the balance sheet of net NaCl absorption.

Many of the apical membrane proteins are expressed in a few other tissues in addition to the intestinal epithelium. In contrast, basolateral membrane transporters are often broadly distributed in the body. In addition to the function of allowing molecules to complete their transcellular transit, such proteins are also utilized frequently (by many cell types) for normal homeostatic processes. For instance, the ubiquitous $Na^+,K^+$-ATPase is responsible for cellular $Na^+$ and $K^+$ homeostasis. It is expressed in the basolateral membrane of intestinal epithelial cells, where it is also responsible for the final step of transcellular sodium absorption.

The major regulator of nutrient absorption is lumenal availability. Although second messengers may modestly increase or decrease the transport rate via absorptive transporters, it is rare to find a normal physiologic state in which absorption of proteins and carbohydrates has been compromised to the extent that the nutrients are not fully absorbed by the end of the small intestine. This does not indicate that absorption succeeds under all conditions. There are a number of disease states in which absorptive processes are compromised directly or net absorption is blunted by the stimulation of secretory processes.

## ABSORPTION OF FAT-SOLUBLE MOLECULES

The major dietary lipids are triacylglycerols (90–95%) with the remainder being free and esterified cholesterol, sterols, and phospholipids. Small amounts (micrograms to milligrams per day) of fat-soluble vitamins (vitamins A, D, E, and K) are also in the diet. Unlike salts and solutes, fats are not ingested in a convenient form for digestion or absorption. Most lipids are water-insoluble, but absorption must occur via an aqueous environment in the lumen. The solution is to transform fats into water-soluble structures through emulsification with amphipathic molecules (dietary proteins, fatty acids, and bile acids secreted into the gut lumen by the liver and gallbladder), followed by digestion via lipases secreted from the pancreas (major source), tongue, and stomach. The finely emulsified fat droplets then spontaneously break down into 4 to 7 nm diameter structures, micelles, with bile salts positioned at the surface and hydrophobic cores that act as a sink for the water-insoluble products of lipolysis (e.g., fatty acids, monoglycerides, and cholesterol) as well as fat-soluble vitamins.

At the mucosal surface, lipids diffuse out of the micelles, so that a saturated aqueous solution of the lipids is maintained in contact with the brush border of the mucosal cells. These lipophilic substances enter the intestinal epithelial cell by diffusion across the plasma membrane. Absorption of lipolytic products is greatest in the upper (proximal) parts of the small intestine, but appreciable amounts are also absorbed in the ileum. Once lipids have diffused from the micelles, bile acids are absorbed in the distal ileum and recycled for another round of fat absorption.

The fate of the fatty acids in enterocytes depends on their size. Fatty acids with less than 10–12 carbon atoms (and some fat-soluble vitamins) transit through the epithelium directly into the portal blood unmodified. Longer-chain FFA and monoglycerides are taken up by the endoplasmic reticulum and metabolically rebuilt into triglycerides. These intracellular lipids are then packaged in 0.5 to 1.0 μm diameter particles termed chylomicrons. The hydrophobic core of chylomicrons contains triglycerides, cholesterol esters, and fat-soluble vitamins. Chylomicrons are carried in secretory vesicles to the basolateral membrane where they are expelled via exocytosis into intercellular spaces at the basal pole of the intestinal epithelial cell. These large particles cannot enter capillaries and instead enter lacteals and are carried in lymphatics to the superior vena cava via the thoracic duct. They are then transported via systemic blood to sites of storage or utilization.

## SECRETION

Transcellular secretion of chloride is the main process leading to fluid secretion in the normal small intestine. Chloride enters enterocytes at the basolateral membrane via the electroneutral $Na^-/K^-/2Cl^-$ cotransporter (gene NKCC1, SLC12A2) and then $Cl^-$ exits the enterocyte via chloride channels in the apical membrane. The product of the cystic fibrosis gene, CFTR (ABCC7), encodes one anion channel in the apical membrane, but other channels may also be important. Transcellular chloride secretion moves a net charge across the epithelial layer, so to maintain cellular electroneutrality, potassium channels in the basolateral membrane allow for charge compensation through $K^+$ efflux. Similarly, it

is believed that $Na^+$ follows chloride passively by paracellular flux through tight junctions to maintain electroneutrality between lumenal and serosal compartments. Water is secreted in response to the net movement of osmolytes (NaCl) into the lumen.

Chloride secretion can be stimulated by increases in cellular cyclic AMP, cyclic GMP, or calcium. A number of membrane receptors for hormones are expressed in the basolateral membrane of enterocytes, which lead to physiologic changes in these second messengers to meet with the demands of absorbing different nutrients. The target of regulation by cyclic nucleotides appears to be the apical CFTR channel. Increased intracellular calcium predominantly increases the activity of the basolateral $K^+$ channel, which stimulates secretion through keeping the cell hyperpolarized (promoting greater efflux of the $Cl^-$ anion) and recycling $K^+$ at the basolateral membrane.

Bicarbonate is secreted by the duodenal epithelium to help neutralize the acidic chyme entering the small intestine from the stomach. Bicarbonate secretion also takes place in the ileum and colon, but its physiologic role in these sites is less clear since pancreatic bicarbonate secretion provides the remaining alkali needed to neutralize lumenal acid. In the duodenum, bicarbonate is secreted by transcellular mechanisms. Carbonic anhydrase acts on intracellular $CO_2$ (coming from either basolateral uptake or cellular metabolism) to produce intracellular $HCO_3^-$ and a proton. The proton leaves the cell via basolateral $Na^+/H^+$ exchange and bicarbonate leaves the duodenal cell either by $Cl^-/HCO_3^-$ exchange or via CFTR channels. This vectorial flux of alkali produces an alkaline shift in pH at the lumen or at a minimum serves to neutralize lumenal acid when $HCO_3^-$ and $H^+$ combine to form $CO_2$ and water. Similar to regulation of chloride secretion, cyclic nucleotides stimulate bicarbonate secretion through enhancing CFTR activity.

## DISEASES OF ABSORPTION AND SECRETION

### Osmotic Diarrhea

Water flows in response to transepithelial movement of osmolytes, in direct response to osmotic gradients. If foodstuffs that cannot be absorbed by the intestinal epithelium are ingested, then they act as an osmotic sponge to pull water into the lumen. This is the mechanism of action of laxatives and is the mechanism underlying many diseases of absorption and secretion (see below). It should be noted that such osmotic diarrhea can also be produced in response to ingesting massive amounts of material that exceed the absorptive capacity of the intestine.

### Infectious Diarrhea

Diarrhea caused by bacteria and other pathogens is responsible for 5 million deaths per year worldwide. Many microorganisms produce enterotoxins that interfere with the second-messenger pathways in enterocytes. Cholera toxin (from *Vibrio cholera*) binds to GM1 gangliosides on the apical surface of intestinal epithelial cells and simulates a sustained increase in intracellular cyclic AMP. This directly inhibits electroneutral NaCl absorption and stimulates chloride secretion. Traveler's diarrhea is caused by STA toxin (*Escherichia coli*), which binds to guanylin receptors on intestinal epithelial cells and increases cyclic GMP, resulting in the stimulation of chloride secretion.

### Disaccharide Intolerance

There is a common genetic variability in levels of lactase, an enzyme in the apical membrane of enterocytes that is responsible for the digestion of carbohydrates. There can also be a genetic sucrase–isomaltase deficiency. Lack of these disaccharidase enzymes will cause osmotic diarrhea when patients ingest carbohydrates. This is because only monosaccharides can be absorbed by enterocytes. The undigested disaccharides thus remain in the lumen.

### Celiac Disease

Celiac disease is a genetic disorder causing a sensitivity to gluten: a water-insoluble protein found in certain cereal grains, notably wheat. In response to gluten, the small intestine undergoes loss of villi, damage to remaining epithelial cells, and crypt hyperplasia. Due to the dramatic loss of absorptive cells on the villi and an abundance of secretory cells in the crypt, the disease results in diarrhea and nonspecific nutrient malabsorption. The underlying cause of the reaction to gluten is unknown.

### Genetic Defects in $Cl^-$ Secretion

Cystic fibrosis is an autosomal recessive disease causing defective intestinal transport through mutation of the CFTR gene and protein. Human mutations in CFTR cause defective $Cl^-$ secretion either by diminishing the amount of CFTR protein in the membrane or by decreasing $Cl^-$ channel opening. Cystic fibrosis causes intestinal obstruction and meconium ileus in newborns, due to poorly hydrated lumenal contents.

Table I also lists the relevant carriers that absorb the majority of NaCl in the absence of other lumenal nutrients. In this mechanism, apical $Na^+/H^+$ exchange mediates sodium uptake into the enterocyte. The concomitant alkalinization of the cell causes activation of $Cl^-/HCO_3^-$ exchange in the same membrane, which mediates chloride uptake. Basolateral $Na^+,K^+$-ATPase promotes $Na^+$ efflux from the cell, completing the transcellular transit of $Na^+$. A basolateral $K^+/Cl^-$ cotransporter (KCC1, SLC12A4) mediates $K^+$ and $Cl^-$ efflux and completes the balance sheet of net NaCl absorption.

Many of the apical membrane proteins are expressed in a few other tissues in addition to the intestinal epithelium. In contrast, basolateral membrane transporters are often broadly distributed in the body. In addition to the function of allowing molecules to complete their transcellular transit, such proteins are also utilized frequently (by many cell types) for normal homeostatic processes. For instance, the ubiquitous $Na^+,K^+$-ATPase is responsible for cellular $Na^+$ and $K^+$ homeostasis. It is expressed in the basolateral membrane of intestinal epithelial cells, where it is also responsible for the final step of transcellular sodium absorption.

The major regulator of nutrient absorption is lumenal availability. Although second messengers may modestly increase or decrease the transport rate via absorptive transporters, it is rare to find a normal physiologic state in which absorption of proteins and carbohydrates has been compromised to the extent that the nutrients are not fully absorbed by the end of the small intestine. This does not indicate that absorption succeeds under all conditions. There are a number of disease states in which absorptive processes are compromised directly or net absorption is blunted by the stimulation of secretory processes.

## ABSORPTION OF FAT-SOLUBLE MOLECULES

The major dietary lipids are triacylglycerols (90–95%) with the remainder being free and esterified cholesterol, sterols, and phospholipids. Small amounts (micrograms to milligrams per day) of fat-soluble vitamins (vitamins A, D, E, and K) are also in the diet. Unlike salts and solutes, fats are not ingested in a convenient form for digestion or absorption. Most lipids are water-insoluble, but absorption must occur via an aqueous environment in the lumen. The solution is to transform fats into water-soluble structures through emulsification with amphipathic molecules (dietary proteins, fatty acids, and bile acids secreted into the gut lumen by the liver and gallbladder), followed by digestion via lipases secreted from the pancreas (major source), tongue, and stomach. The finely emulsified fat droplets then spontaneously break down into 4 to 7 nm diameter structures, micelles, with bile salts positioned at the surface and hydrophobic cores that act as a sink for the water-insoluble products of lipolysis (e.g., fatty acids, monoglycerides, and cholesterol) as well as fat-soluble vitamins.

At the mucosal surface, lipids diffuse out of the micelles, so that a saturated aqueous solution of the lipids is maintained in contact with the brush border of the mucosal cells. These lipophilic substances enter the intestinal epithelial cell by diffusion across the plasma membrane. Absorption of lipolytic products is greatest in the upper (proximal) parts of the small intestine, but appreciable amounts are also absorbed in the ileum. Once lipids have diffused from the micelles, bile acids are absorbed in the distal ileum and recycled for another round of fat absorption.

The fate of the fatty acids in enterocytes depends on their size. Fatty acids with less than 10–12 carbon atoms (and some fat-soluble vitamins) transit through the epithelium directly into the portal blood unmodified. Longer-chain FFA and monoglycerides are taken up by the endoplasmic reticulum and metabolically rebuilt into triglycerides. These intracellular lipids are then packaged in 0.5 to 1.0 μm diameter particles termed chylomicrons. The hydrophobic core of chylomicrons contains triglycerides, cholesterol esters, and fat-soluble vitamins. Chylomicrons are carried in secretory vesicles to the basolateral membrane where they are expelled via exocytosis into intercellular spaces at the basal pole of the intestinal epithelial cell. These large particles cannot enter capillaries and instead enter lacteals and are carried in lymphatics to the superior vena cava via the thoracic duct. They are then transported via systemic blood to sites of storage or utilization.

## SECRETION

Transcellular secretion of chloride is the main process leading to fluid secretion in the normal small intestine. Chloride enters enterocytes at the basolateral membrane via the electroneutral $Na^+/K^+/2Cl^-$ cotransporter (gene NKCC1, SLC12A2) and then $Cl^-$ exits the enterocyte via chloride channels in the apical membrane. The product of the cystic fibrosis gene, CFTR (ABCC7), encodes one anion channel in the apical membrane, but other channels may also be important. Transcellular chloride secretion moves a net charge across the epithelial layer, so to maintain cellular electroneutrality, potassium channels in the basolateral membrane allow for charge compensation through $K^+$ efflux. Similarly, it

is believed that $Na^+$ follows chloride passively by paracellular flux through tight junctions to maintain electroneutrality between lumenal and serosal compartments. Water is secreted in response to the net movement of osmolytes (NaCl) into the lumen.

Chloride secretion can be stimulated by increases in cellular cyclic AMP, cyclic GMP, or calcium. A number of membrane receptors for hormones are expressed in the basolateral membrane of enterocytes, which lead to physiologic changes in these second messengers to meet with the demands of absorbing different nutrients. The target of regulation by cyclic nucleotides appears to be the apical CFTR channel. Increased intracellular calcium predominantly increases the activity of the basolateral $K^+$ channel, which stimulates secretion through keeping the cell hyperpolarized (promoting greater efflux of the $Cl^-$ anion) and recycling $K^+$ at the basolateral membrane.

Bicarbonate is secreted by the duodenal epithelium to help neutralize the acidic chyme entering the small intestine from the stomach. Bicarbonate secretion also takes place in the ileum and colon, but its physiologic role in these sites is less clear since pancreatic bicarbonate secretion provides the remaining alkali needed to neutralize lumenal acid. In the duodenum, bicarbonate is secreted by transcellular mechanisms. Carbonic anhydrase acts on intracellular $CO_2$ (coming from either basolateral uptake or cellular metabolism) to produce intracellular $HCO_3$ and a proton. The proton leaves the cell via basolateral $Na^+/H^+$ exchange and bicarbonate leaves the duodenal cell either by $Cl^-/HCO_3^-$ exchange or via CFTR channels. This vectorial flux of alkali produces an alkaline shift in pH at the lumen or at a minimum serves to neutralize lumenal acid when $HCO_3^-$ and $H^+$ combine to form $CO_2$ and water. Similar to regulation of chloride secretion, cyclic nucleotides stimulate bicarbonate secretion through enhancing CFTR activity.

## DISEASES OF ABSORPTION AND SECRETION

### Osmotic Diarrhea

Water flows in response to transepithelial movement of osmolytes, in direct response to osmotic gradients. If foodstuffs that cannot be absorbed by the intestinal epithelium are ingested, then they act as an osmotic sponge to pull water into the lumen. This is the mechanism of action of laxatives and is the mechanism underlying many diseases of absorption and secretion (see below). It should be noted that such osmotic diarrhea can also be produced in response to ingesting massive amounts of material that exceed the absorptive capacity of the intestine.

### Infectious Diarrhea

Diarrhea caused by bacteria and other pathogens is responsible for 5 million deaths per year worldwide. Many microorganisms produce enterotoxins that interfere with the second-messenger pathways in enterocytes. Cholera toxin (from *Vibrio cholera*) binds to GM1 gangliosides on the apical surface of intestinal epithelial cells and simulates a sustained increase in intracellular cyclic AMP. This directly inhibits electroneutral NaCl absorption and stimulates chloride secretion. Traveler's diarrhea is caused by StA toxin (*Escherichia coli*), which binds to guanylin receptors on intestinal epithelial cells and increases cyclic GMP, resulting in the stimulation of chloride secretion.

### Disaccharide Intolerance

There is a common genetic variability in levels of lactase, an enzyme in the apical membrane of enterocytes that is responsible for the digestion of carbohydrates. There can also be a genetic sucrase–isomaltase deficiency. Lack of these disaccharidase enzymes will cause osmotic diarrhea when patients ingest carbohydrates. This is because only monosaccharides can be absorbed by enterocytes. The undigested disaccharides thus remain in the lumen.

### Celiac Disease

Celiac disease is a genetic disorder causing a sensitivity to gluten: a water-insoluble protein found in certain cereal grains, notably wheat. In response to gluten, the small intestine undergoes loss of villi, damage to remaining epithelial cells, and crypt hyperplasia. Due to the dramatic loss of absorptive cells on the villi and an abundance of secretory cells in the crypt, the disease results in diarrhea and nonspecific nutrient malabsorption. The underlying cause of the reaction to gluten is unknown.

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### Genetic Defects in $Cl^-$ Absorption

Congenital chloride diarrhea (CLD) is an extremely rare, recessive, autosomal genetic disorder that produces $Cl^-$-rich, acidic diarrhea commencing at birth. The transport defect is limited to the ileum and colon. The gene that causes congenital chloride diarrhea (DRA, SLC26A3) encodes a transmembrane protein that can perform $Cl^-/HCO_3^-$ exchange when the protein is normal, but cannot transport $Cl^-$ when DRA contains mutations found in patients suffering from CLD.

### Genetic Defects in $Na^+$-Dependent Sugar Absorption

Glucose–galactose malabsorption is a rare, autosomal recessive disorder in which $Na^+$-coupled uptake of glucose and galactose is defective. Sugar ingestion leads to osmotic diarrhea, which can be treated by eliminating glucose and galactose from the diet. Mutations in the SGLT1 protein, mediating $Na^+$-dependent sugar uptake at the apical membrane, have been shown to be the basis for at least a portion of glucose–galactose malabsorption cases.

### See Also the Following Articles

**Carbohydrate and Lactose Malabsorption • Carbohydrate Digestion and Absorption • Celiac Disease • Diarrhea • Diarrhea, Infectious • Epithelial Barrier Function • Epithelium, Proliferation of • Epithelium, Repair of • Fat Digestion and Absorption • Malabsorption • Small Intestinal Motility • Water-Soluble Vitamins: Absorption, Metabolism, and Deficiency**

### Further Reading

Barrett, K. E., and Donowitz, M. (eds.) (2002). "Gastrointestinal Transport: Molecular Physiology, Current Topics in Membranes," Vol. 50, Chapters 2, 6–8, 10, 12, and 13. Academic Press, New York.

Johnson, L. R. (ed.). (1994). "Physiology of the Gastrointestinal Tract," 3rd Ed., pp. 1271–1453, Chapters 50–62. Raven Press, New York.

Yamada, T. (ed.). (1999). "Textbook of Gastroenterology," 3rd Ed., Chapter 15. Lippincott, Williams & Wilkins, New York.

# Small Intestine, Anatomy

GAËLLE BOUDRY, PING-CHANG YANG, AND MARY H. PERDUE
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**enteric nervous system** Neural elements distributed within the wall of the digestive tract and organized in two plexuses: myenteric and submucosal. This system can function independently of the central nervous system, to coordinate gastrointestinal function, or can interact with the extrinsic nervous system, acting as the first level of integration.

**enterocytes** Major cell type in the intestinal epithelium. These tall and columnar cells are highly differentiated to fulfill absorptive and secretory functions and also form a barrier against penetration of bacteria and dietary antigens into the mucosa.

**mucosa** Layer of the small intestine in contact with the luminal contents. It is formed by upward "villus" projections into the lumen surrounded by downward "crypt" invaginations.

**muscularis externa** Smooth muscle layer surrounding the mucosa and submucosa. It is composed of an inner circular and outer longitudinal layer, which function in coordination to propel and mix luminal contents.

**Peyer's patches** Organized lymphoid aggregates disseminated along the small intestine in the mucosa and submucosa; contain functional T and B lymphocytes as well as specialized epithelial microfold cells, which sample luminal antigens and bacteria.

**The small intestine is a convoluted tube ranging from 3 to 9 m in length, depending on the tone and the degree of stretch induced during measurement. It extends from the pylorus to the large intestine at the ileocecal junction. It is classically divided into three segments, the duodenum, jejunum, and ileum. Although regional differences exist**

**within the small intestine, the general structure is similar throughout its length.**

## GROSS ANATOMY

The following discussions focus on the anatomy and histology of two segments of the small intestine, the jejunum and the ileum.

### External and Internal Appearance

The jejunum starts right after the duodenojejunal flexure, a configuration that is supported by a fibromuscular band, the ligament of Treitz, which is attached to the diaphragm. The jejunum and ileum lie in coils in the abdominal and pelvic cavities, suspended in a fan-shaped manner by the mesentery, from the posterior abdominal wall. The distance from the posterior abdominal wall to the intestinal wall varies from about 15 to 20 cm, increasing distally. This architecture allows each coil to accommodate to changes in form and position. The jejunum and ileum are not separated by any distinct anatomic landmark, but several features become gradually more apparent from proximal to distal. Classically, the proximal 40% of the mobile small intestine is designated as the jejunum and the distal 60% as the ileum.

The internal surface of the jejunum and proximal ileum shows numerous transverse folds (the plicae circulae, or valves of Kerchkring). These mucosal and submucosal folds are permanent structures, varying from 3 to 10 mm in height and running transversely around the small intestine. Their number gradually decreases through the distal jejunum and they may be entirely absent from the distal ileum. Small lymphoid nodules, the Peyer's patches, of varying size are also apparent at regular intervals. They become more numerous distally and form a large, continuous antimesenteric Peyer's patch in the distal ileum.

### Blood and Lymph Supply

From the ligament of Treitz to the ileocecal junction, the small intestine is supplied by a dozen or more branches arising from the left branch of the superior mesenteric artery. These branches run between the two folds of the peritoneum composing the mesentery. As they approach the intestinal wall, they branch and anastomose with one another to form a series of arcades or arches. The straight arteries arising from the final arches send branches to either side of the intestine and encircle it. In turn, these arterial circles emit branches of diminishing size, which penetrate the intestinal wall. Veins accompanying the arterial vessels supplying the jejunum and ileum drain into the superior mesenteric vein, which merges with the splenic vein to form the portal vein. Lymph nodes are arranged in three groups: one near the intestinal wall, one at the level of the arterial arcades, and the third along the upper part of the superior mesenteric artery. These nodes and those in the intestinal wall interconnect by many lymphatic vessels.

### Innervation

The parasympathetic nerve supply of the small intestine comes from the dorsal nucleus of the vagus. The fibers from these cell bodies enter the abdominal cavity as the anterior and posterior vagal trunks with the esophagus and pass into the wall of the gut with its blood vessels via the celiac and superior mesenteric ganglia, in which these fibers do not synapse. The fibers end in the intestinal wall, where they synapse with cell bodies in the submucosal and myenteric plexuses. The sympathetic preganglionic fibers have their cell bodies in the spinal cord segment T9 and T10 and enter the sympathetic trunk by white rami communicantes. They leave as the splanchnic nerves and pass the celiac and superior mesenteric ganglia, where they synapse. Postganglionic fibers enter the small intestine with its blood vessels.

## SEROSA

The jejunum and ileum are almost completely enveloped by a thin extension of the peritoneum, a monolayer of flattened mesothelial cells and loose connective tissue (Fig. 1). The only exception is the mesenteric border, where the peritoneal folds are separated to allow the entry and exit of blood vessels, lymphatics, and nerves. These latter ramify in a subserosal zone of connective tissue lying between the mesothelial layer and the muscularis externa.

## MUSCULARIS EXTERNA

The muscularis externa (or propria) consists of an outer longitudinal and an inner circular layer of smooth muscle separated by the myenteric plexus (the plexus of Auerbach) (Fig. 1). Smooth muscle cells are densely packed in characteristics bundles and packets, separated by small spaces consisting mainly of collagen fibrils and larger spaces occupied by nerves, capillaries, interstitial cells of Cajal, and intramuscular septa of connective tissue. Intestinal smooth muscle cells are uninucleated and spindle-shaped cells measuring

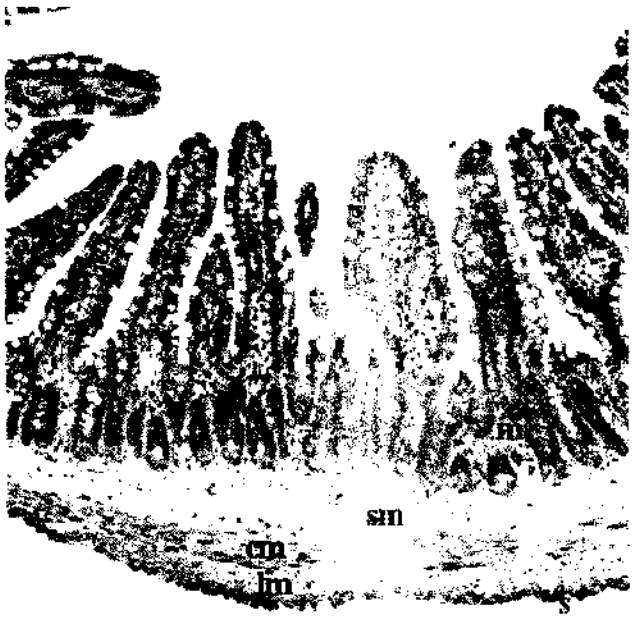


FIGURE 1 Transverse section of rat jejunum (× 200). The wall of the small intestine can be divided in four different layers: the mucosa (m), facing the lumen; the submucosa (sm); the two layers of circular (cm) and longitudinal (lm) muscles forming the muscularis externa; and the serosa (s).

500–700 μm in length at rest but are able to shorten to less than a quarter of their resting length when contracting. Important features of smooth muscle cells are cell-to-cell junctions (intermediate and gap junctions) involving specializations of the membrane between two adjacent cells. These junctions are essential to produce mechanical and electrical cooperation and communication between cells, which form a muscular syncitium. The intestinal muscular layers and the circular layer, in particular, are richly innervated. There are no classical neuromuscular junctions, rather intramuscular axons tend to run parallel to the smooth muscle cells, sending varicosities from which neurotransmitters are released. Commonly found associated with smooth muscle cells and nerve varicosities are the interstitial cells of Cajal, which communicate with both types of cells. Other cells possibly located within smooth muscle layers are macrophages, mast cells, and myoblast-like cells.

The myenteric plexus, as well as the submucosal plexus located in the submucosa (discussed later), are the two major integrative systems of the enteric nervous system. Plexuses are networks of wide and thin ganglia interconnecting through neuronal processes. Ganglia are composed of two cell types, nerve cells and glial cells, associated with a neuropil formed by closely packed neuronal and glial processes. Each ganglion and the connecting strands are surrounded by a basal lamina and collagen fibrils. Small blood vessels can lie near but do not enter ganglia of the myenteric plexus. Neural connections exist between the myenteric and the submucosal plexuses as well as with extrinsic neurones.

## SUBMUCOSA

The submucosa extends from the muscularis externa to the mucosa (Fig. 1). It consists of connective tissue, blood and lymphatic vessels, and the submucosal plexus (plexus of Meissner). The submucosa may also contain scattered migratory cells, of which mast cells are frequently the predominating cell type. Relatively large arterioles, venules, and lymphatic vessels form extensive networks within the submucosa. From these networks, numerous penetrating capillary vessels supply and drain most of the mucosa and muscularis externa. These dense vascular networks enable the submucosa to play a role in vascular routing and related distribution of regional blood and lymphatic flow. The composition of the submucosal plexus is similar to that of the myenteric plexus. However, in humans, and contrary to the composition in rodents, this plexus is composed of two distinct layers, the inner and outer submucosal plexuses. The submucosal plexus has smaller ganglia, less neurons, and a less compact network compared to the myenteric plexus.

## MUCOSA

### Architecture

The mucosa is composed of three components: the muscularis mucosae, which delimit the mucosa from the submucosa, the lamina propria, and the epithelial cells, which face the intestinal lumen. A transverse section from any part of the small intestine reveals the unique architecture of the small intestinal mucosa, involving the crypts and villi that cover the entire length of the small intestine. The straight and tubelike crypts (crypts of Lieberkühn) are downward projections of the epithelium into the lamina propria whereas the villi are upward leaflike or fingerlike projections of the surface epithelium and the lamina propria. Villi and crypts are contiguous, in that the epithelium composing these two structures is continuous. However, the number of villi is considerably less than the number of crypts because several crypts may open into a single mouth and more than one mouth can open between two adjacent villi. Fingerlike villi predominate in the jejunum and ileum whereas leaflike villi are more common in the duodenum. The villi are tallest (about 0.8–1 mm) in

the distal part of the duodenum and the proximal jejunum but become progressively shorter. Moreover, jejunal and ileal villi differ also by the series of indentations along the side of the villi, which are marked in the proximal small intestine but disappear in the terminal ileum.

## Vascular Pattern of the Intestinal Villi

The vascular pattern of the intestinal villi is essentially the same from the duodenum to the ileum. Each villus is supplied by a central artery, which runs through the center of the villus toward the tip. It then divides into two narrow arterial trunks, which run directly below the epithelial cells downward toward the base of the villus. These arteries give rise to capillary branches that form a dense anastomosing network extending between the arterial trunks and the two veins, which drain each villus. Each intestinal villus contains also a central blind-ended lymph vessel, the lacteal.

## Mucosal Components

### *Muscularis Mucosa*

The muscularis mucosa is the outermost layer of the mucosa. It is composed of elastic fibers and 3–10 smooth muscle cells, generally arranged in an outer longitudinal and inner circular layer. Smooth muscle cells may radiate from the muscularis mucosa into the lamina propria and extend in the villi.

### *Lamina Propria*

The lamina propria forms the connective tissue core of the villi and surrounds the crypt epithelium. The crypt and villus epithelial cells and the lamina propria are separated by a distinct basement membrane composed of an ultrastructurally apparent basal lamina and a deeper network of collagenous fibers. The lamina propria is composed of noncellular connective tissue elements, i.e., collagen and elastin, blood and lymphatic vessels, and myofibroblasts supporting villi. However, the main characteristic of the lamina propria is to contain numerous immunologically competent cells as well as nerve endings. The most numerous cell types are mononuclear cells, plasma cells, and lymphocytes. Plasma cells contain immunoglobulin (IgA or IgM) and are concentrated more in the intercrypt region. Lymphocytes, both B and T cells, are found throughout the lamina propria but often form more dense infiltrates just above the muscularis mucosae. Other cell types are more sparsely distributed, including eosinophils, macrophages, and mast cells. However, macrophages are mostly located along the superior part of the lamina propria near the tip of the villi. Numerous nerves endings are present in the lamina propria, many of which are in close contact with mast cells.

### *Epithelium*

The four major cell types of the epithelium (enterocytes, goblet, endocrine, and Paneth cells) arise from stem cells, which divide continuously, located just above the crypt base. Differentiation and maturation occur in 5–6 days as the cells migrate from the crypt to the villus tips, where they are subsequently sloughed into the lumen (Fig. 2).

**Crypt epithelium** The most abundant cell types in the crypts are undifferentiated enterocytes. However, crypts also contain two distinct cell types, Paneth cells and endocrine cells. Paneth cells do not migrate and are located within the crypt base. Their number increases from the duodenum to the ileum. They derive from undifferentiated crypt cells and seem to undergo replacement at a relatively slow rate. They have a pyramidal shape, the nucleus being located in the basal half of the cell. Their outstanding feature is their content of secretory granules of the zymogen variety, located in the cytoplasm between the nucleus and the apical border of the cell. As secretory cells, Paneth cells show rough endoplasmic reticulum and extensive Golgi apparatus. They contain lysozyme, immunoglobulin, and defensin and seem capable of phagocytic activity, suggesting a role in the regulation of the intestinal microbial flora.

Endocrine cells are relatively abundant in the crypts, although they are also present in the villi. They are of two morphological types, either "open," with a pyramidal

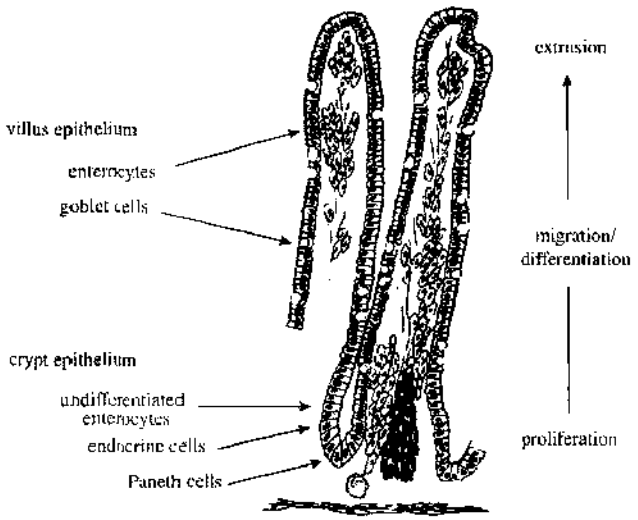


**FIGURE 2** Schematic diagram of rat jejunal mucosa, illustrating the different types of cells encountered in the epithelium.

shape and connection with the lumen, or "closed," with a spindle shape and no connection with the lumen. Secretory granules are concentrated in the basal part of the cytoplasm whereas Golgi apparatus elements are supranuclear. The apical surface shows regular tufts of microvilli longer than those of enterocytes (described later). At least 16 distinct types of endocrine cells have been described along the small intestine, each with a characteristic regional distribution and composition.

**Villus epithelium** Enterocytes are the major villus epithelial cell type. They are highly specialized tall and columnar cells, with an oval nucleus located basally (Fig. 3). The usual organelles are all represented: the endoplasmic reticulum is not prominent but the Golgi apparatus is, the mitochondria are usually long and filamentous, and a number of pinocytic vesicles may be seen near the apical region. The apical surface is composed of microvilli and glycocalyx. Microvilli are close projections of cytoplasm covered by the cell membrane. They are about 1 μm high and 0.1 μm in diameter, providing a 14- to 40-fold increase in the apical surface area.

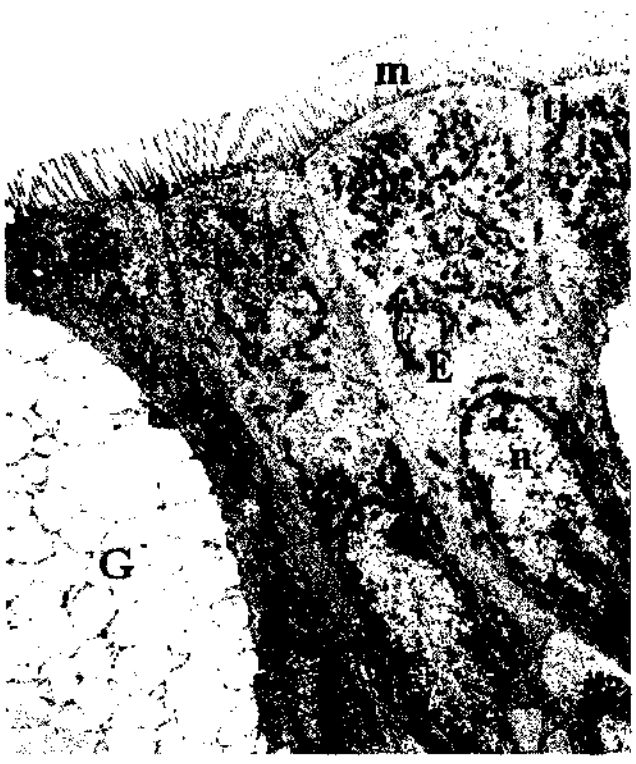


FIGURE 3 High-magnification micrograph of rat villus epithelial cells (× 3000). Enterocytes (E) are tall columnar cells with an oval, basally located nucleus (n). Their characteristic features are the presence of microvilli (m), which enhance apical surface area, and a tight junction (tj), allowing a tight and continuous junction between two adjacent cells. Goblet cells (G) are mucous-secreting cells interspersed among enterocytes.

The glycocalyx is a thin, filamentous layer of mucopolysaccharide material, housing important enzymes that function in terminal digestive processes. Enterocytes (and the other epithelial cells) are surrounded at their apical side by typical 0.5- to 2-μm intercellular junctional complexes. They consist of two distinct structures, the tight junction and the adherens junction, that encircle the cells as a belt, allowing a tight and continuous contact between two adjacent cells. These two structures are associations of transmembrane and cytoplasmic proteins linked with the cytoskeleton.

Goblet cells are interspersed among the enterocytes. They are polarized, mucous-secreting cells, increasing in number distally. They are easily recognizable by their pear-shaped region containing the mass of mature mucigen granules. Often a small "puff" of mucous can be distinguished emerging from the apex. Apical microvilli are sparse and irregular in size and shape. Cytoplasmic organelles, including a well developed network of rough endoplasmic reticulum, free ribosomes, mitochondria, and lysosomes, lie around the mass of mucous granules. Last, intraepithelial lymphocytes, mainly T cells, lie between individual epithelial cells, usually just above the basement membrane. The ratio of epithelial cells to intraepithelial lymphocytes is about 6:1.

## PEYER'S PATCHES

Peyer's patches are distinct small lymphoid nodules located along the antimesenteric border. Their number increases distally. They are composed of lymphoid follicles that are located in the mucosa but that may also extend into the submucosa. Follicles are composed of a lymphoid nodule with a germinal center, a follicle-associated epithelium, and a dome, situated between these two structures. The germinal center contains mainly IgA-positive B cells. It is surrounded by the dome, populated by B lymphocytes, macrophages, and plasma cells. Facing the lumen is the follicle-associated epithelium, which contains few goblet cells and epithelial cells specialized in the transport of luminal antigens, the microfold cells (M cells). These cells are different from enterocytes in that they have short microvilli and no glycocalyx at the apical side. Moreover, their basolateral membrane is invaginated to form a pocket containing immunocompetent cells.

### See Also the Following Articles

Circulation, Overview • Duodenum, Anatomy • Enteric Nervous System • Gastrointestinal Tract Anatomy, Overview •

**Interstitial Cells of Cajal • Gastrointestinal Matrix, Organization and Significance**

## Further Reading

Madara, J. L., and Trier, J. S. (1994). The functional morphology of the mucosa of the small intestine. *In* "Physiology of the Gastrointestinal Tract" (L. R. Johnson, ed.), 4th Ed., pp. 1577–1622. Raven Press, New York.

Porter, E. M., Bevins, C. L., Ghosh, D., and Ganz, T. (2002). The multifaceted Paneth cell. *Cell. Mol. Life Sci.* 59, 156–170.

Segal, G. H., and Petras, R. E. (1997). Small intestine. *In* "Histology for Pathologists" (S. S. Sternberg, ed.), 2nd Ed., pp. 495–518. Lippincott-Raven Publ., Philadelphia.

Timmermans, J. P., Hens, J., and Adriaensen, D. (2001). Outer submucous plexus: An intrinsic nerve network involved in both secretory and motility processes in the intestine of large mammals and humans. *Anat. Rec.* 262, 71–78.

Van Itallie, C. M., and Anderson, J. M. (2001). Molecular structure and regulation of tight junctions. *Curr. Top. Membr.* 50, 163–186.

Van Kruiningen, H. J., West, A. B., Freda, B. J., and Holmes, K. A. (2002). Distribution of Peyer's patches in the distal ileum. *Inflamm. Bowel Dis.* 8(3), 180–185.

# Small Intestine, Benign and Malignant Neoplasms of the

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**ampulla of Vater** The orifice in the duodenum through which the common bile duct and pancreatic duct drain.

**celiac sprue** Intestinal malabsorption disease characterized by diarrhea and malnutrition, caused by immune-mediated gluten sensitivity.

**Crohn's disease** A disease of chronic inflammation potentially involving any portion of the gastrointestinal tract but with a propensity for the terminal ileum. The etiology of this disease is incompletely understood.

**familial adenomatous polyposis (FAP)** An inherited syndrome in which thousands of polyps develop in the colon, as well as in the stomach and upper intestine (duodenum). Bony tumors, known as osteomas, and other soft tissue tumors can also occur (Gardner's variant).

**Peutz-Jeghers syndrome** Familial syndrome consisting of mucocutaneous pigmentation and gastrointestinal polyp (usually harmartomas) formation.

**Tumors of the small intestine are rare, accounting for only 1% of all gastrointestinal (GI) neoplasms, even though the small intestine accounts for 90% of the surface area and 75% of the length of intestinal tract. Approximately 5300 new cases of small intestinal malignancies are diagnosed each year. Two-thirds of small bowel neoplasms are malignant and these account for approximately 2% of all GI malignancies. The most common malignancies of the small bowel are adenocarcinomas, carcinoid tumors, lymphomas, and sarcomas. There is a slight male predominance and the average age at disease presentation is 55–60 years. This article will discuss malignant and benign small bowel neoplasms.**

## PATHOGENESIS

Tumors of the small bowel can form from any of the cells that are found in this organ. Adenomas and adenocarcinomas develop from epithelial and glandular tissue, lymphomas develop from lymphocytes found in lymphoid tissue, sarcomas develop from smooth muscle, and carcinoid tumors arise from the Kulchitsky

cell, an enterochromaffin cell located in the crypts of Leiberkuhn.

Many theories have been proposed to explain the low rate of malignancy in the small bowel as compared to the colon and stomach:

1. liquid contents of the small bowel cause less mucosal irritation and dilute carcinogens;
2. rapid transit of small bowel contents decreases exposure to carcinogens;
3. decreased bacterial load in the small bowel (especially anaerobic bacteria) results in less conversion of bile acids into carcinogens;
4. benzpyrene, a known carcinogen found in food, is converted to less toxic metabolites by benzpyrene hydrolase, which is found in higher concentrations in the small intestine than in the stomach and colon; and
5. increased lymphoid tissue and secretory immunoglobulin A found in the small bowel may be protective against cancer formation.

## PREDISPOSING CONDITIONS

Many diseases have known associations with small bowel neoplasms:

1. Crohn's disease is a risk factor for adenocarcinoma of the small bowel.
2. Celiac disease is associated with lymphoma and adenocarcinoma.
3. Patients with Peutz-Jeghers syndrome have hamartomas in the jejunum or ileum which may undergo malignant transformation.
4. Patients with FAP have increased rates of small bowel adenomas, especially in the duodenum.

## CLINICAL PRESENTATION

Patients with small bowel malignancies often present late in the course of the disease, when the tumor has spread beyond the point of cure. The most common symptoms are abdominal pain, intestinal obstruction, intussusception, gastrointestinal bleeding, palpable abdominal mass, anorexia, and weight loss. Over 50% of benign small bowel tumors remain asymptomatic, whereas 70–90% of malignant tumors lead to symptoms. With malignant tumors, abdominal pain is the most common symptom, present in as many of 80% of patients. Weight loss and anorexia occur in approximately half of patients with malignant tumors and 25% of patients develop intestinal obstruction. Benign tumors lead to gastrointestinal (GI) bleeding more commonly than malignant tumors (29% versus 6%). Abdominal pain, often fluctuating in nature, is the most common symptom of benign lesions.

## DIAGNOSIS

Diagnosing small bowel neoplasms is often difficult due to the rarity of the disease and the nonspecific nature of signs, symptoms, and physical exam findings. It is important to consider a small bowel neoplasm in patients with unexplained abdominal pain, weight loss, or occult GI bleeding. Late detection of small bowel tumors is common, with the average time from onset of symptoms to diagnosis being 5 months. Up to 50% of patients will have metastatic disease at presentation. Unfortunately, early detection and treatment are the most significant variables for favorable outcome in these patients.

Patients suspected of having a small bowel neoplasm should undergo a complete history and physical examination, fecal occult blood testing, a complete blood count, measurement of serum electrolytes, and liver function tests.

Radiographic examination is often employed in the evaluation of suspected small bowel tumors. Plain films of the abdomen are of little use unless the lesion has led to intestinal obstruction. Upper GI series with small bowel follow-through (SBFT) are commonly ordered and can show mass lesions in over 50% of patients. A superior test but one that is more technically difficult to perform is enteroclysis, a double-contrast study performed by inserting a tube in the duodenum and infusing barium. The sensitivity of enteroclysis is approximately 90% versus 50% for SBFT. Computed tomography (CT) is not effective for detecting small intralumenal or mucosal tumors, but is excellent at detecting metastasis, especially to the liver. CT enteroclysis is performed by placing a tube in the proximal small bowel and infusing barium while obtaining CT images. The accuracy of this study for detecting small bowel tumors is still being determined.

Endoscopy is often useful in the diagnosis of small bowel tumors. Esophagogastroduodenoscopy (EGD) can visualize only to the second to third portion of the duodenum, limiting its usefulness. EGD is good for evaluating patients with FAP for duodenal adenomas or adenocarcinomas. Lesions past the ligament of Treitz are more difficult to reach with an endoscope. Push enteroscopy, a type of upper endoscopy using a longer than normal endoscope, can allow the user to visualize up to 60 cm of proximal jejunum. A newer technique for visualizing the small intestine is wireless capsule endoscopy. In this method, the patient swallows a capsule

that takes video images as it passes through the length of the small intestine. Capsule endoscopy will likely be helpful in diagnosis of small intestinal tumors, and experience with this technique is growing.

## MALIGNANT LESIONS OF THE SMALL INTESTINE

### Small Bowel Adenocarcinoma

Adenocarcinoma is the most common type of malignant small bowel carcinoma, constituting 40–50% of small bowel cancers. Approximately 50% of small bowel adenocarcinomas occur in the duodenum, especially at the ampulla of Vater, whereas 30% form in the jejunum and 20% occur in the ileum. The higher concentrations of bile acids and their metabolites in the duodenum have been postulated to explain the increased incidence of carcinoma in this portion of bowel. Adenocarcinomas usually occur between the ages of 50 and 70, with a male:female ratio of approximately 1.4 : 1. Risk factors include Crohn's disease; high animal fat intake; heavy consumption of red meat, salt-cured foods, and smoked foods; prior peptic ulcer disease; FAP; prior colon cancer; celiac sprue; and cystic fibrosis.

Early adenocarcinoma of the small bowel is usually asymptomatic, as with other small bowel lesions. When symptoms occur, they are usually nonspecific. A high degree of suspicion is often required to make an early diagnosis. If the lesion is in the duodenum, endoscopy can be utilized to make a diagnosis.

Surgical intervention provides the only hope for cure in patients with adenocarcinoma of the small bowel. Patients with lesions in the first or second part of the duodenum should undergo pancreaticoduodenectomy (Whipple procedure). Tumors occurring in the distal duodenum, jejunum, or ileum may be treated with wide local excision with lymphadenectomy. Prognosis is determined by resectability, pathologic status of resected margins, histologic grade, and presence or absence of lymph node involvement. Lesions confined to mucosa and submucosa have a good prognosis, whereas lesions that invade through the serosa have a very poor prognosis. The overall 5-year survival rate ranges from 20 to 35%. Small bowel adenocarcinomas are generally considered to be radio-resistant and thus radiation therapy does not appear to be effective. To complicate matters, the small bowel cannot tolerate high doses of radiation without sustaining significant injury. For these reasons, radiotherapy is not widely used for these tumors. Chemotherapy has been used to treat these tumors, but due to the low incidence of small bowel adenocarcinoma, literature on its effectiveness is lacking.

### Carcinoid Tumors

Carcinoid tumors are a rare type of neuroendocrine tumor that can be located in the stomach, small intestine, colon, or rectum, although they are most common in the ileum and appendix. Carcinoid tumors make up approximately 40% of primary small bowel malignancies.

These tumors arise from the Kulchitsky cell, an enterochromaffin cell located in the crypts of Lieberkuhn. Grossly, these tumors appear yellow, due to their high lipid content, and are firm. Carcinoid tumors are usually slow-growing and are often diagnosed incidentally. Inflammation with shortening and thickening of the mesentery, the so-called desmoplastic reaction, can lead to intestinal obstruction due to kinking of the intestine. Tumor cells often secrete bioactive products, such as serotonin, which can lead to carcinoid syndrome in approximately 10% of patients. Symptoms of carcinoid syndrome include diarrhea, flushing, and hypotension. Surgery to completely remove the tumor and any involved lymph nodes is considered the best treatment.

### Primary Small Bowel Lymphomas

Lymphomas are solid malignancies of lymphoid tissue. Lymphomas often arise in lymph nodes; however, lymphomas may also arise in extranodal sites, with the GI tract being the most common location for extranodal involvement. The diagnosis of primary GI lymphoma requires that no peripheral lymphadenopathy be present, that the patient have a normal white blood cell count, that tumor involvement be predominantly in the GI tract, and that there is no involvement of the liver or spleen. Approximately 10% of GI tract lymphomas arise in the small intestine. The incidence of small bowel lymphoma peaks in the seventh decade of life and there is a slight male predominance. Most tumors arise in the distal small bowel, most likely because there is more lymphoid tissue in these areas, especially in the terminal ileum. Predisposing conditions for small bowel lymphoma include autoimmune disease, immunodeficiency syndromes (especially acquired immunodeficiency syndrome), immunosuppressive therapy after organ transplantation, Crohn's disease, celiac disease, and radiation therapy. Patients most often present with abdominal pain, weight loss, anorexia, and, less commonly, gastrointestinal bleeding or iron deficiency anemia.

There are many types of small intestinal lymphomas. The B-cell lymphomas include marginal B-cell lymphomas, diffuse large B-cell lymphomas, mantle cell lymphoma, follicular lymphoma, and Burkitt's lymphoma. Immunoproliferative small intestinal disease (IPSID), also known as α heavy-chain disease or Mediterranean lymphoma, is a B-cell lymphoma that occurs mainly in the Middle East. This lymphoma is most common in the second or third decade of life. IPSID usually occurs in patients of lower socioeconomic class. There is an association between infectious agents, such as *Giardia lamblia*, and IPSID. Treatment of early-stage disease often consists of antibiotic therapy alone, although chemotherapy is needed for more advanced cases.

The most common T-cell lymphoma is enteropathy-associated intestinal T-cell lymphoma. This lymphoma is a complication of celiac sprue, a genetic disease characterized by gluten sensitivity. These tumors often arise in the jejunum. This tumor should be considered in patients with celiac sprue who are adhering to a strict gluten-free diet but have persistent symptoms of diarrhea and weight loss.

Treatment for small intestinal lymphomas usually include a combination of surgery and chemotherapy. Surgery alone results in a cure for approximately 30% of patients. The overall 5-year survival for small intestinal lymphomas is approximately 20–30%, depending on the type of tumor.

### Sarcomas

Sarcomas are malignant tumors that arise from smooth muscle tissue and can occur anywhere in the body where smooth muscle is present. Sarcomas account for 10% of small bowel tumors. The most common type of small bowel sarcoma is the leiomyosarcoma, with less common varieties including fibrosarcoma, liposarcoma, and angiosarcoma. Small bowel sarcomas tend to grow slowly and are usually large at presentation, with many being greater than 5 cm in size. Signs and symptoms at presentation include weight loss, gastrointestinal bleeding, bowel perforation, or palpable mass on abdominal exam. These tumors often grow extralumenally and therefore bowel obstruction is a rare presentation. Sarcomas look very similar to leiomyomas, a benign smooth muscle tumor, and it can be hard to tell the difference between them, even on histological examination. Criteria for malignancy include the following: more than two mitoses per high-powered field; nuclear atypia; and necrosis. Treatment for sarcomas is surgery. Sarcomas rarely metastasize to lymph nodes, so lymph node resection is usually not indicated and will not improve survival. Chemotherapy and radiation therapy have not shown benefit. Survival is approximately 50% at 5 years.

### Metastatic Lesions

Even though primary small bowel carcinomas are quite rare, the small intestine is a relatively common site for metastatic disease. Malignant melanoma commonly metastasizes to the small intestine, with 60% of patients with melanoma having gastrointestinal metastases. Primary carcinomas from the breast, lung, and kidney can also metastasize to the small intestine.

## BENIGN SMALL INTESTINAL TUMORS

### Adenomas

Adenomas of the small intestine can be villous or tubular. Villous adenomas have significant malignant potential. Up to 40% of villous adenomas are found to have malignant cells within them when removed. Periampullary villous adenomas may require a Whipple procedure for resection. Tubular adenomas have lower malignant potential.

### Leiomyomas

Leiomyomas are firm, are gray or white in color, and arise from the submucosal layer. On endoscopy, they appear as submucosal lesions with normal overlying mucosa. These tumors consist of well-differentiated smooth muscle cells. Like sarcomas, these lesions often grow extralumenally and therefore can achieve a large size before they are discovered. Central necrosis of the lesion can occur when the tumor outgrows its blood supply, which may lead to ulceration and bleeding into the bowel lumen.

### Lipomas

Lipomas are benign tumors that consist mainly of fat. They usually occur in the submucosal layer and have normal overlying mucosa. They are most commonly found in the ileum and jejunum.

### See Also the Following Articles

**Cancer, Overview • Celiac Disease • Crohn's Disease • Familial Adenomatous Polyposis (FAP) • Hamartomatous Polyposis Syndromes • Lymphomas**

### Further Reading

Cusack, J. (2002). Diagnosis and management of small bowel neoplasms. UpToDate, Version 10.3. Available at www.uptodate.com.

Cusack, J. (2002). Epidemiology, clinical features, and types of small bowel neoplasms. UpToDate, Version 10.3. Available at www.uptodate.com.

DiSario, J., Randall, W., Vargas, H., and McWhorter, W. (1994). Small bowel cancer: Epidemiological and clinical characteristics from a population-based registry. *Am. J. Gastroenterol.* 89, 699–701.

Lance, P. (1999). Tumors and other neoplastic diseases of the small intestine. *In* "Textbook of Gastroenterology" (T. Yamada, ed.), 3rd Ed., Vol. 2, pp. 1722–1738. Lippincott, Williams & Wilkins, Philadelphia, PA.

Neugut, A., Marvin, M., Rella, V., and Chabot, J. (1997). An overview of adenocarcinoma of the small intestine. *Oncology* 11, 529–536.

Rustgi, A. (2002). Small intestinal neoplasms. *In* "Sleisenger & Fordtran's Gastrointestinal and Liver Disease" (M. Feldman, L. Friedman, and M. Sleisenger, eds.), 7th Ed., Vol. II, pp. 2169–2172. W. B. Saunders, Philadelphia, PA.

# Small Intestine, Development

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**crypt–villus axis morphogenesis** Formation of the crypt–villus unit, the principal functional component of the small intestine.

**endodermal specification** Process by which the endoderm forms; distinct from the ectodermal and mesodermal layers of the early embryo.

**homeobox genes** Transcription factors that contain a homeobox or homeodomain, a conserved nucleotide sequence that encodes a DNA binding domain.

**The small intestine is a complex epithelial-lined tubular organ that grows to ~6 m in length in the adult human. It is a heterogeneous tissue that exhibits regional differences in morphology and function along the horizontal axis (from duodenum to ileum) and along the vertical axis (from crypt to villus tip). Its epithelium is derived from the primitive endoderm, and connective tissue, muscle, and hematopoietic components are mesodermal in origin. The duodenum, up to the opening for the common bile duct (ampulla of Vater), is derived from the foregut (which also gives rise to the liver, lungs, and pancreas). The midgut gives rise to the duodenum beyond the ampulla, and includes the jejunum, ileum, and large bowel, up to and including the proximal transverse colon.**

## EMBRYOLOGY OF THE SMALL INTESTINE

The gastrointestinal epithelium is derived from the embryonic endoderm, and the smooth muscle, hematopoietic elements, and connective tissue are derived from mesoderm. The endoderm, ectoderm, and mesoderm are formed during gastrulation, which occurs in the human by week 3 of gestation. During this process, the primitive streak appears in the bilaminar germ disk of the blastocyst, which is suspended between the yolk sac and amnion. Cells migrate ventrally and laterally, forming the three germ layers. The gut tube forms and closes as the endodermal layer folds. In rodents, folding begins as the anterior intestinal portal forms at the anterior tip of the endoderm. Cells located at this portal move posteriorly. The caudal intestinal portal similarly emerges at the posterior endodermal tip, and cells located at this position move anteriorly. The gut tube closes as a result of this folding process. The foregut and hindgut initially form closed sacs, but the midgut communicates with the yolk sac, by the vitelline duct. Aberrant persistence of this duct leads to the congenital anomaly called Meckel's diverticulum. The endoderm contacts ectoderm at the closed ends of the foregut and hindgut, and fuses to form the buccopharyngeal and cloacal membranes.

By weeks 4–5 the gut tube elongates rapidly, and by week 7, this expansion forces its herniation into the umbilicus. By weeks 8–9, intestinal villi have formed. As the gut returns to the abdominal cavity by week 10, it undergoes a complex series of rotational events (Fig. 1). This rotation and subsequent migration of the cecum to the right lower quadrant results in the proper anatomic location of the small and large bowels.

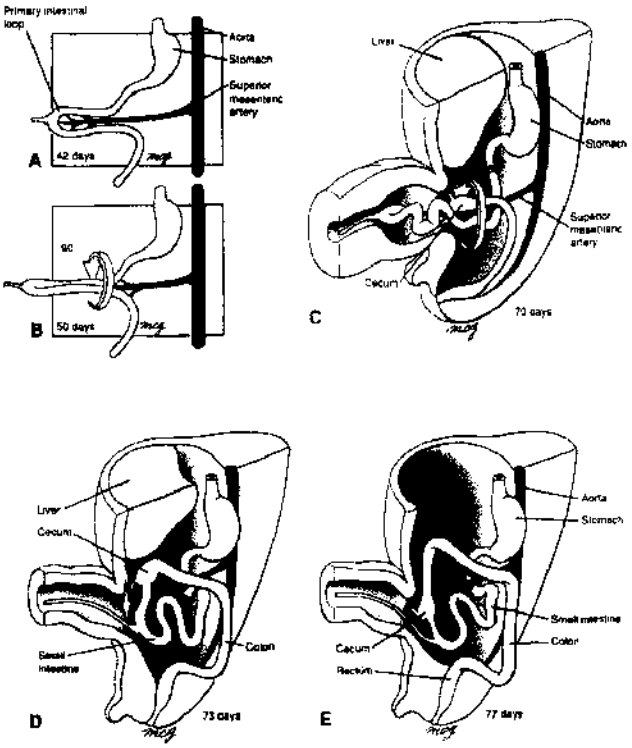


FIGURE 1 Intestinal growth, herniation, and rotation. (A, B) At the end of the sixth week, the primary intestinal loop herniates into the umbilicus, rotating through 90° counterclockwise. (C) The small intestine elongates to form jejunal-ileal loops, the cecum and appendix grow, and at the end of the 10th week, the primary intestinal loop retracts into the abdominal cavity, rotating an additional 180° counterclockwise. (D, E) During the 11th week, the retracting midgut completes this rotation as the cecum is positioned just inferior to the liver. The cecum is then displaced inferiorly, pulling down the proximal hindgut to form the ascending colon. The descending colon is simultaneously fixed on the left side of the posterior abdominal wall. (Reprinted with permission from Larsen, W. J. (1997). "Human Embryology," p. 241. W. B. Saunders Co.

## IN THE BEGINNING: EARLY SPECIFICATION OF THE ENDODERM AND FOLDING/FORMATION OF THE GUT TUBE

How is the early endodermal layer formed, distinct from mesoderm and ectoderm? An explosion of information about the regulation of early endodermal specification has come from studies in organisms such as the frog (*Xenopus laevis*), the zebrafish (*Danio rerio*), and the mouse, although many parts of the mammalian puzzle still remain unsolved. A cascade of regulatory transcription factors appears to be responsible for this process. Genes related to *Xenopus VegT*, a "T box" transcription factor, are likely to be at the top of the transcriptional regulatory hierarchy, activating Nodal signaling and other transforming growth factor-β (TGF-β) family proteins, and inducing expression of proteins such as xSox17α, the Mix-like paired homeodomain proteins and GATA proteins. Fibroblast growth factors, members of the Wnt growth factor family, and retinoic acid are soluble factors involved in gastrulation. Experiments in knockout (null) mice, in which specific genes have been deleted to determine their function in early embryonic life, have shown the critical role of some of these transcription factors. For example, *Mixl1* null (*Mixl1*−/−) mice exhibit a thickened primitive streak, arrested embryo development, and absent heart tube and gut, among other abnormalities. Another important set of proteins belongs to the hepatic nuclear factor 3 (HNF3) family, which are involved in endodermal differentiation at later stages of development. Many of these proteins play multiple roles in the early embryo (for example, in anterior–posterior pattern formation and the establishment of left–right asymmetry), thus it is likely that cell-specific differences in receptor populations, concentrations of morphogens, and dosage over time, as well as space, may determine the specific end result of their actions.

The next step in the process of gut morphogenesis is folding and formation of the gut tube. GATA-4 and several of the bone morphogenetic proteins appear to be important regulators in mice. For example, *Gata4*−/− mice exhibit abnormal ventral morphogenesis, lacking a primitive foregut and heart tube. The bone morphogenetic proteins (BMP-2, -4, -5, and -7) are expressed in the anterior intestinal portal and are required for proper folding of the embryo. These events have not been studied in the human.

### Regional Differentiation in the Small Bowel

The molecular factors that regulate regional specification along the horizontal axis of the small intestine and colon (from duodenum to rectum) are the subject of intensive investigation. An important class of candidate genes is the homeobox-containing (*hox*) transcription factors, which are involved in the specification of body pattern and which are expressed in specific regions of the gut mesenchyme during embryonic development (Fig. 2). The *hox* genes are also expressed in the adult human small intestine. These genes demonstrate spatial colinearity; i.e., the pattern of expression along the body axis reflects the chromosomal order of the genes. Their importance in small bowel ontogeny has been demonstrated in knockout mice or by experiments in which *hox* genes are "misexpressed" in an aberrant location (i.e., more caudal or ventral than the normal expression pattern). For example, targeted deletion of *Hoxd12* or

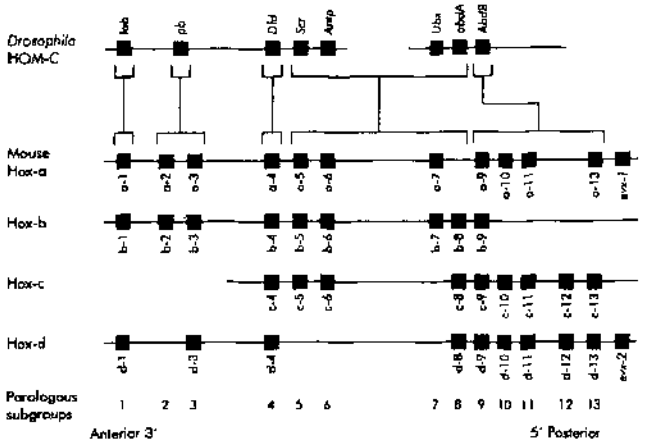


FIGURE 2 Diagrammatic representation of the *HOM-C* complex in *Drosophila* and its phylogenetic homology in the form of four *Hox* paralogues. Reproduced from Beck, F. (2002). Homeobox genes in gut development. *Gut* 51, p. 451. With permission from the BMJ Publishing Group.

*Hoxd13* produces anal sphincter anomalies, and deletion of the *Hoxd4-d13* gene cluster yields abnormalities in the ileocecal valve and the pylorus, as well as the anal sphincter. Virally mediated misexpression of *Hoxd13* in midgut mesoderm, (which is normally expressed in hindgut mesoderm) induces a hindgut endodermal phenotype. These fascinating experiments indicate the importance of the *hox* genes in normal gut morphogenesis and support the critical role of mesenchymal–endodermal interactions in determining cell fate (see later).

Members of the related *Para-hox* gene cluster (which are dispersed homeobox-containing genes), are also important in gut patterning and organ specification. Just as the *Para-hox* gene *Pdx1* has been shown to play a critical role in pancreatic and duodenal development, members of the *Cdx* family, particularly *Cdx2*, have a crucial role in small bowel epithelial differentiation. *Cdx2−/−* (null) mice die at implantation; however, *Cdx2+/−* (heterozygous) mice develop hamartomatous lesions in the small bowel and colon. These lesions contain gastric mucosa from various parts of the stomach, including squamous forestomach epithelium, suggesting that the development of a proximal gastric epithelium is a "default pathway" that is followed when *Cdx2* is absent. *Cdx* genes may also regulate the expression of *hox* genes. *Cdx2* expression persists into adulthood, when it clearly plays a role in the terminal differentiation of the gut epithelium (see later).

The hedgehog signaling pathway has been implicated in gut morphogenesis, as a mediator of endoderm–mesenchyme interactions. Mice in which the *Sonic hedgehog* (*Shh*) gene, or in which its downstream transcriptional regulators, Gli 2 and Gli 3, have been deleted, show abnormalities in foregut formation, with anomalies in lung, trachea, and esophagus formation. *Shh* null mice also show reduced intestinal smooth muscle, gut malrotation, annular pancreas, intestinal transformation of the stomach, duodenal stenosis, and imperforate anus. Ectopic expression of *Shh* induces *Bmp4* and *Hoxd13* expression and results in muscle hypertrophy in the gut, suggesting a role in radial (from villus tip to smooth muscle/serosa) differentiation.

## CRYPT–VILLUS AXIS FORMATION, EPITHELIAL–MESENCHYMAL INTERACTIONS, AND EPITHELIAL CELL DIFFERENTIATION

### Crypt–Villus Axis Morphogenesis

The principal anatomic and functional (absorptive) unit of the small intestine is the crypt–villus axis (Fig. 3). The crypts of Lieberkuhn contain presumptive gut epithelial stem cells that are the source of the four

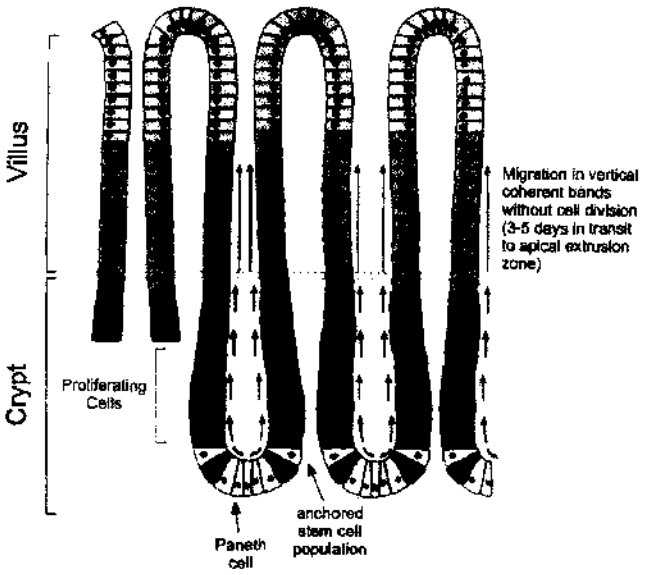


FIGURE 3 Model of organization of the small intestinal crypt–villus axis. The small intestinal crypt contains approximately 250 cells. Anchored stem cells (white) are located in the lower crypt and give rise to proliferating daughter cells that migrate up toward the villus. These differentiate into enterocytes, goblet cells, and enteroendocrine cells. Paneth cells also arise from the stem cell and differentiate during downward translocation to the base. Senescent cells are extruded near the villus tips. Reproduced with permission from Rubin, D. C. (1999). Small intestine: Anatomy and structural anomalies. *In* "Textbook of Gastroenterology" (Yamada, T., Alpers, D. H., Laine, L., Owyang, C., and Powell, D. W., eds.). 3rd Ed., Vol. 2, pp. 1561–1583. Copyright Lippincott Williams and Wilkins. Adapted from Gordon, J. I. (1989). Intestinal epithelial differentiation: New insights from chimeric and transgenic mice. *J. Cell Biol.* 108, 1187.

major cell types of the gut mucosa. The stem cells, located near the base of the crypts, give rise to proliferating daughter cells in the midcrypt region; daughter cells in turn migrate onto the villus to become terminally differentiated (nonproliferating) absorptive enterocytes, mucus-secreting goblet cells, or enteroendocrine cells, or to the bottom of the crypt to become Paneth cells. Two additional, rarer cell types thought to arise from the same stem cell are the epithelial M cell, which overlies Peyer's patches, and the tuft or caveolated cell, a villus-associated cell.

The small intestinal epithelial crypt–villus axis is formed in humans by week 12 of gestation. The complex process of crypt–villus morphogenesis begins with marked proliferation of the undifferentiated endoderm and surrounding mesenchyme of the gut tube. The endoderm and mesenchyme become stratified, and then undergo a remodeling process that results in the formation of a lumen and villi. This proceeds over time in a rostral-to-caudal direction. Intestinal villi form by weeks 8–9, followed by the crypts by weeks 10–12. Mesenchymal cells invaginate into the endoderm to form crypts and villi. Cells with the appropriate morphologic characteristics of enterocytes, goblet cells, enteroendocrine, and Paneth cells can be identified by week 12. Before birth, the villus-associated enterocytes acquire all the brush border enzymes (e.g., sucrase–isomaltase, lactase, and peptidases) and transporters (for glucose, fructose, etc.) required for normal nutrient absorption. Hormonal factors such as glucocorticoids, and growth factors such as epidermal growth factor and the TGF-β family, are likely to play an important tropic and maturational role.

## Epithelial–Mesenchymal Interactions

Many years of experimentation have shown that mesenchymal–epithelial interactions are critical for the formation of the crypt–villus axis. For example, primitive endoderm cannot differentiate in culture without the presence of mesenchyme. Endoderm and mesoderm have inductive capabilities (i.e., each can direct the differentiation of the other tissue in coculture models). As indicated previously, Shh–BMP signaling from endoderm to mesenchyme is important in early gut formation. The requirement for mesenchyme in the maintenance of the crypt–villus axis has been confirmed by studies of Forkhead 6 (Fkh 6; now Foxl1), Nkx2.3, and epimorphin, indicating that the absence of these mesenchymal factors dramatically alters the normal morphology of the crypts and villi.

## Crypt Stem Cells and Epithelial Cell Differentiation

Precise isolation and identification of the intestinal crypt stem cell have remained elusive, because, unlike other progenitor cells, such as the hematopoietic stem cell, genetic markers have yet to be characterized. However, some of the factors that maintain the crypt's proliferative compartment have been discovered. The Wnt/β-catenin/adenomatous polyposis coli (APC) signaling pathway, critically important in colon carcinogenesis, also appears to be required for the maintenance of the normal crypt–villus axis. Mice with deletion of the gene encoding Tcf-4, a member of the Tcf/Lef family of hydroxymethylglutaryl coenzyme A (HMG) box transcription factors that are downstream effectors of this pathway, show the absence of proliferative compartments in the prospective crypt region. Mice with this defect die soon after birth. A fascinating study has provided some insight into how cellular compartmentalization and migration along the crypt–villus axis are also regulated by this pathway. β-Catenin/T cell factor (TCF) complexes regulate the expression of ephrin B (EphB) receptor tyrosine kinases. Mice containing null mutations for both the EphB2 and EphB3 receptors show inappropriate mixing on the villus of proliferative cells, which are normally strictly confined to the crypts. The migration of Paneth cells to the base of the crypt also appears dependent on EphB receptor tyrosine kinases, because deletion of the EphB3 receptor tyrosine kinase results in localization of Paneth cells on the villi as well as in the crypts.

A key challenge for the future is to delineate the pathways that determine how intestinal stem cells commit to become enterocytes, enteroendocrine, Paneth, or goblet cells. Evidence indicates that the Notch signaling pathway plays an important role in this process. Targeted deletion in mice of a component of the Notch signaling pathway, called Math 1, produces a crypt–villus axis that contains only enterocytes, suggesting that expression of Math 1 forces the stem cell into a "prosecretory" phenotype (Paneth, enteroendocrine, and goblet cells are secretory cells). Another member of this pathway, Hes1, appears to function as a basal inhibitor of enteroendocrine cell differentiation. It has been hypothesized that high levels of Notch expression induce increased Hes1 expression, which in turn inhibits Math 1, thus leading to the "default" enterocytic pathway. Finally, the *Para-hox* gene *Cdx2* has a crucial role in enterocytic differentiation. It is expressed in the developing and the adult gut. When transfected into a cryptlike epithelial cell line, it induces an enterocyte-like phenotype. *Cdx2* also regulates the expression of a

variety of enterocyte-specific genes, such as sucrase–isomaltase.

In conclusion, although the descriptive embryology of the human small intestine has been well characterized, its molecular basis is still the subject of intensive investigation. Studies using sophisticated techniques to analyze gut development in transgenic and knockout mice, as well as in *Drosophila*, zebrafish, and *Xenopus*, have provided a wealth of new information. These studies plus knowledge of the human genome should soon permit the identification of the molecular basis of a variety of intestinal birth defects.

## See Also the Following Articles

**Development, Overview • Large Intestine, Development**

## Further Reading

Babyatsky, M. W., and Podolsky, D. K. (1999). Growth and development of the gastrointestinal tract. *In* "Textbook of Gastroenterology" (T. Yamada, D. H. Alpers, L. Laine, C. Owyang, and D. W. Powell, eds.), 3rd Ed., Vol. 1, pp. 547–584. Lippincott Williams & Wilkins, Philadelphia.

Batlle, E., Henderson, J. T., Beghtel, H., van den Born, M. M. W., Sancho, E., Huls, G., Meeldijk, H., Robertson, J., van de Wetering, M., Pawson, T., and Clevers, H. (2002). β-Catenin and TCF mediate cell positioning in the intestinal epithelium by controlling the expression of EphB/ephrinB. *Cell* 111, 251–263.

Beck, F. (2002). Homeobox genes in gut development. *Gut* 51, 450–454.

De Santa Barbara, P., Van Den Brink, G. R., and Roberts, D. J. (2002). Molecular etiology of gut malformations and diseases. *Am. J. Med. Genet. (Semin. Med. Genet.)* 115, 221–230.

Korinek, V., Barker, N., Moerer, P., van Donselaar, E., Huls, G., Peters, P. J., and Clevers, H. (1998). Depletion of epithelial stem-cell compartments in the small intestine of mice lacking Tcf-4. *Nat. Genet.* 19, 379–383.

Montgomery, R. K., Mulberg, A. E., and Grand, R. J. (1999). Development of the human gastrointestinal tract: Twenty years of progress. *Gastroenterology* 116, 702–731.

Roberts, D. J. (2000). Molecular mechanisms of development of the gastrointestinal tract. *Dev. Dynam.* 219, 109–120.

Rubin, D. C. (1999). Small intestine: Anatomy and structural anomalies. *In* "Textbook of Gastroenterology" (T. Yamada, D. H. Alpers, L. Laine, C. Owyang, and D. W. Powell, eds.), 3rd Ed., Vol. 2, pp. 1561–1583. Lippincott Williams & Wilkins, Philadelphia.

Shivdasani, R. A. (2002). Molecular regulation of vertebrate early endoderm development. *Dev. Biol.* 249, 191–203.

Wells, J. M., and Melton, D. A. (1999). Vertebrate endoderm development. *Annu. Rev. Cell Dev. Biol.* 15, 393–410.

Yang, Q., Bermingham, N. A., Finegold, M. J., and Zoghbi, H. Y. (2001). Requirement of Math1 for secretory cell lineage commitment in the mouse intestine. *Science* 294, 2155–2158.

Chronic gastroesophageal reflux leads to the formation of intestinal metaplasia or Barrett's esophagus. Patients with Barrett's esophagus may develop dysplasia with an increased risk for esophageal adenocarcinoma. Smoking increases the amount of gastroesophageal reflux predisposing to Barrett's esophagus. Smokers with Barrett's are at increased risk of developing adenocarcinoma. The risk rises with the amount and duration of smoking and does not decrease until 30 years postcessation. Tobacco use is definitely responsible for esophageal squamous cell cancer and adenocarcinoma.

Gastric adenocarcinoma is twice as common in heavy smokers, current smokers, and those that started smoking at a younger age.

Cigarette smoking is a risk factor for the development of colorectal adenomas and colorectal carcinoma, most markedly after 20 years of use. Also, it is associated with increased risk of mortality in both men and women with colon cancer.

The most important environmental risk factor strongly associated with pancreatic cancer is smoking. The risk rises with increased amounts of smoking and decreases to that of the normal population 15 years after cessation of smoking. Pancreatic tumors have been found after long-term consumption of tobacco-specific nitrosamines in drinking water.

In hepatocellular carcinoma, smoking as a risk factor is controversial, but most of the current evidence suggests that it has a minor role.

## See Also the Following Articles

**Barrett's Esophagus • Colitis, Ulcerative • Duodenal Ulcer • Esophageal Cancer • Gastric Ulcer • Gastroesophageal Reflux Disease (GERD) • *Helicobacter pylori* • Pouchitis**

## Further Reading

Ashley, M. (1997). Smoking and diseases of the gastrointestinal system: An epidemiological review with special reference to sex differences. *Can. J. Gastroenterol.* 11, 345–352.

Boyko, E., and Koepsell, T. (1987). Risk of ulcerative colitis among former and current smokers. *N. Engl. J. Med.* 316, 707–710.

Calkins, B. (1989). A meta-analysis of the role of smoking in inflammatory bowel disease. *Digest. Dis. Sci.* 34, 1841–1854.

Hensrud, D., and Heimburger, D. (1998). Diet, nutrients, and gastrointestinal cancer. *Gastroenterol. Clin. North Am. Clin. Nutr.* 27, 325–346.

Kahrilas, P., and Gupta, R. (1990). Mechanisms of acid reflux associated with cigarette smoking. *Gut* 31, 4.

Kato, I., and Nomura, A. (1992). A prospective study of gastric and duodenal ulcer and its relation to smoking, alcohol, and diet. *Am. J. Epidemiol.* 135, 521–530.

Kurata, J., and Nogawa, A. (1997). Meta-analysis of risk factors for peptic ulcer: Non-steroidal anti-inflammatory drugs, *Helicobacter pylori*, and smoking. *J. Clin. Gastroenterol.* 24, 2–17.

Pullan, R., and Rhodes, J. (1994). Transdermal nicotine for active ulcerative colitis. *N. Engl. J. Med.* 330, 811–815.

United States Department of Health and Human Services (1990). "The Health Benefits of Smoking Cessation." A Report of the Surgeon General DHHS Publication No. (CDC) 90–8416. United States Department of Health and Human Services, Office of Smoking and Health, Rockville, MD.

# Solitary Rectal Ulcer Syndrome

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**Delorme procedure** Perineal approach to the repair of rectal procidentia in which there is circumferential mucosectomy followed by longitudinal plication of the rectal wall, and mucosal reapproximation.

**internal intussusception** Rectal intussusception in which the lead point remains above the pelvic floor (also called occult prolapse).

**intussusception** Invagination or prolapse of one segment of bowel into the lumen of the immediately adjacent segment.

**rectal procidentia** Circumferential full-thickness intussusception of the rectum in which the lead point of the intussusception descends through the anal canal.

**rectopexy** Fixation by suture or prosthetic mesh of the mobilized rectum to the presacral fascia (to prevent rectal intussusception).

**solitary rectal ulcer syndrome** Condition that is clinically characterized by a disturbance of defecation, blood and mucus per rectum, and abnormalities of the rectal wall ranging from erythema to polyp formation to ulceration; histologically characterized by obliteration of the lamina propria by fibromuscular proliferation derived from the muscularis mucosae, thickening of the muscularis mucosae, and sometimes misplaced mucosal glands deep to the muscularis mucosae.

Solitary rectal ulcer syndrome (SRUS) is a spectrum of clinicopathological abnormalities of uncertain etiology. The condition is poorly understood and even the name is misleading—the lesion on the rectal wall may be neither solitary nor ulcerative. The essential features of the syndrome are a disturbance of defecation, the passage of blood and mucus per rectum, and abnormalities of the rectal wall, ranging from erythema to polyp formation and ulceration. There is an association of SRUS with failure of relaxation of the pelvic floor during defecation, with internal intussusception of the rectum, and with overt rectal prolapse. Optimal therapy of SRUS is unclear, and the role of surgery is primarily guided by the presence or absence of either overt or occult (internal intussusception) rectal prolapse. In fact, the understanding of SRUS and the management of this condition may be enhanced by recognizing two discrete entities—SRUS with and without intussusception of the rectal wall.

## CLINICAL FEATURES

Solitary rectal ulcer syndrome (SRUS) affects men and woman approximately equally, although some studies have found a female predominance. It is most often seen in young adults, but the condition has presented in children as well as in patients over the age of 60 years. The typical symptoms are straining at evacuation of stool, often for prolonged periods of time, a feeling of incomplete rectal emptying, and the passage of blood and mucus per rectum. Fecal incontinence is rare, but mucus leakage is common. Many patients resort to self-digitation either to aid evacuation or, less commonly, to relieve a sense of obstruction. The percentage of patients who suffer anorectal, perineal, or lower abdominal pain is highly variable. Most series report delays in diagnosis of several years.

The symptoms and signs are closely linked to the presence or absence of overt rectal prolapse, which is present in about 25% of patients. The general physical examination is unremarkable, but anorectal evaluation is always abnormal. On straining, roughly half of the patients will show marked perineal descent. In patients with overt rectal prolapse, the symptoms and physical findings of prolapse may predominate, including fecal incontinence and a low tone, patulous anus. In the absence of overt rectal prolapse, anal tone and squeeze are likely to be normal. Digital rectal examination may reveal induration and thickening of the rectal wall, or a polypoid mass may be felt. The lesion is usually mobile on the underlying muscle.

Sigmoidoscopy is abnormal and may reveal a wide range of findings. The classical ulcer is shallow with a whitish base, a thin erythematous rim, and with normal surrounding mucosa. The ulcers may vary in size, shape, number, and location. The lesions are multiple in about one-third of cases. A polypoid lesion may be present in 25% of the cases, and in some patients, there may only be patchy, granular erythema of the mucosa. The changes of SRUS are most frequently seen anteriorly, but may occur at any point on the rectal wall, even circumferentially. The usual level is between 6 and 10 cm from the anal verge but may occur from 4 to 15 cm. Confluent

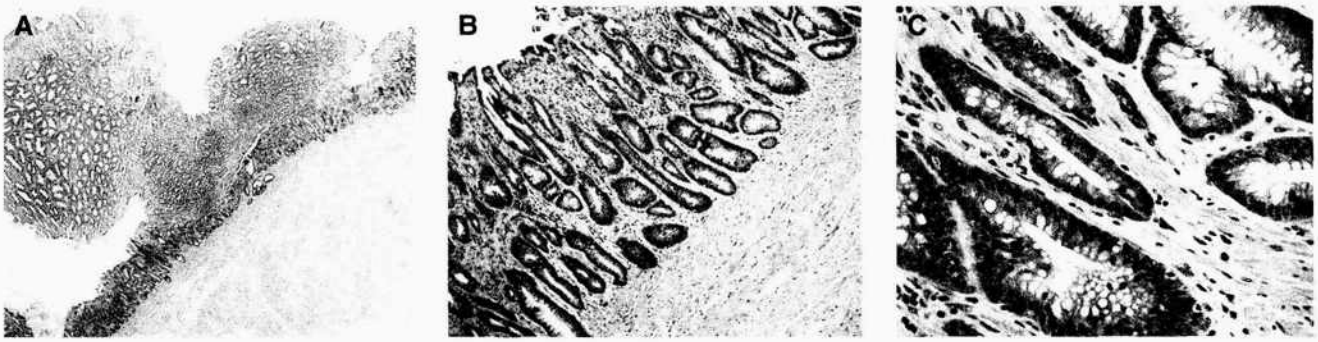


FIGURE 1 (A) Overview of SRUS with a polypoid mucosa. (B) Detail of mucosa, showing a hyaline-like lamina propria with fibromuscular replacement of the lamina propria and a markedly thickened muscularis mucosae. (C) Detail of the loss of inflammatory cells in the lamina propria, with bundles of smooth muscle fibers running parallel to the crypts.

circumferential changes may rarely produce rectal stenosis.

## HISTOLOGY

Biopsies must be taken to confirm the diagnosis. These should be taken from the edge of an ulcer or from the hyperemic or polypoid mucosa. The main histologic features are obliteration of the lamina propria by fibromuscular proliferation of the muscularis mucosae, muscle fibers streaming up between the crypts, thickening of the muscularis mucosae (Fig. 1), and misplaced mucosal glands deep to the muscularis mucosae. Similar findings have been described in biopsies of prolapsing mucosa occurring elsewhere in the gastrointestinal tract when prolapse occurs. In the large bowel, these include "ostomy" sites, hemorrhoids and inflammatory cloacogenic polyps (which are virtually identical to SRUS but occur at the dentate line), and around the orifices of diverticula.

Complications that occur are most frequently superficial erosions or ulcers that can bleed (Fig. 2A), ischemia with a typical pseudomembrane and fibrin thrombi in the superficial capillaries, and reactive changes in the underlying epithelium (Fig. 3). If there is hemorrhage into the stalk, there may be misplaced glands in the submucosa similar to that found in the overlying mucosa although without the features of prolapse (colitis cystica profunda), and often accompanied by surrounding lamina propria, hemorrhage, and hemosiderin-laden macrophages. Immediately beneath mucosae with ulceration or erosions, the crypts may have a stellate or serrated appearance similar to that found in hyperplastic polyps (Fig. 2B). Sometimes the reactive changes may be very marked and mimic adenomatous change; proliferation to the surface may occur. The biopsies shown in Fig. 4 are deemed sufficiently adenoma-like that the patient is being followed regularly to ensure that there is no progression, because the natural history of unusual changes such as these is unknown. There is, of course, no reason why adenomas should not occur in SRUS, but typical adenomas appear to be exceedingly rare.

## INVESTIGATIONS

The diagnosis of SRUS is made by history, physical examination, endoscopy, and biopsy. Radiologic and physiologic studies are of minimal diagnostic value. However, investigations may help to define the pathogenesis of this condition in an individual patient and

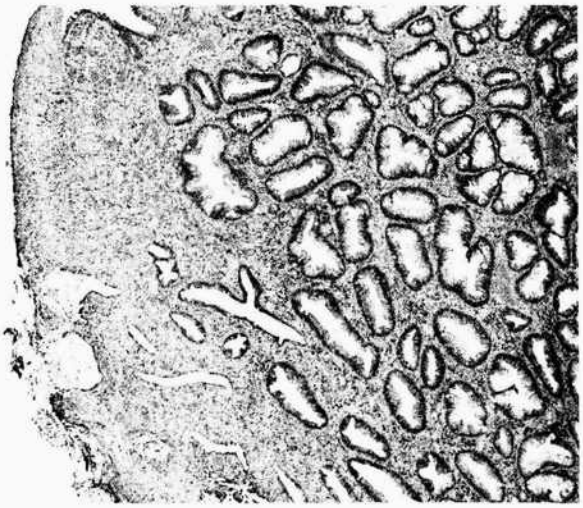

FIGURE 2 Area with superficial ulceration (left). Note that the crypts immediately beneath the ulcerated surface can take on an appearance that mimics that seen in a hyperplastic polyp with serrated crypts, a nonspecific pattern that can occur beneath any ulcerated surface in the large bowel.

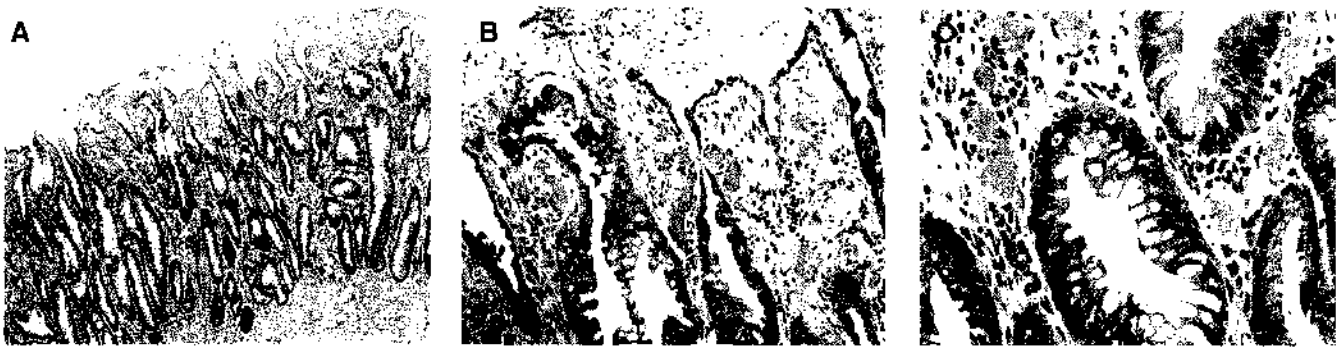


FIGURE 3 (A) Ischemic changes with a superficial pseudomembrane are common. (B) Detail of pseudomembrane and fibrin thrombi in capillaries. (C) Reactive changes in underlying epithelium and fibrin thrombi in capillaries.

may aid in therapeutic planning. The colon should be evaluated to exclude coexisting pathology.

### Defecating Proctography

Evacuation proctography (defecography) can demonstrate abnormal rectal mechanics during defecation, including failure of the anorectal angle to open, incomplete emptying of the rectum, perineal descent, and intussusception of the rectal wall, with the intussusception remaining above the pelvic floor (occult rectal prolapse or internal intussusception) or exiting via the anus (overt rectal prolapse).

### Physiologic Studies

The results of physiologic studies have been variable. Physiologic parameters correlate with the presence or absence of rectal prolapse and the degree of prolapse. Anal manometry has been reported to be normal, or to demonstrate reduced resting and squeeze pressures, primarily related to whether overt rectal prolapse is present. Pudendal neuropathy, perineal descent, and inability to expel a rectal balloon are all common findings. Electrophysiological studies have demonstrated failure of puborectalis muscle relaxation and inappropriate contraction of the puborectalis muscle during attempts at rectal evacuation.

### Endoanal Ultrasound

Characteristic findings are thickening of the muscularis propria and an indistinct transition between the mucosa and muscularis propria. Thickening of the internal sphincter is commonly seen. Less frequently, the submucosa and external sphincter may also appear to be thickened. Ultrasound may also be used to confirm nonrelaxation of the puborectalis.

## PATHOGENESIS

The etiology of SRUS is unknown, and it is likely that there are a variety of causes. Two factors appear to predominate, nonrelaxation (or paradoxical contraction) of the puborectalis muscle and rectal prolapse. The evidence suggests that patients with nonrelaxing puborectalis and patients with prolapse are distinct clinical groups and that there is not a progression from "spastic pelvic floor" to rectal intussusception, or from internal intussusception to overt full-thickness prolapse.

Straining against a nonrelaxing pelvic floor may predispose to a cascade of direct trauma to the mucosa against the closed anal canal, mucosal prolapse, mucosal ischemia, and mucosal ulceration. Nonrelaxing puborectalis has been described in one-half to three-fourths of patients with SRUS. The incidence of overt or occult rectal prolapse is highly variable in the literature; a degree of prolapse may be seen in 80% of patients with SRUS.

Direct trauma from self-digitation has been suggested as a causative factor, but this seems very unlikely; lesions are often located beyond the reach of a finger, many patients who self-digitate do not develop the syndrome, and cessation of self-digitation does not lead to mucosal healing.

## TREATMENT

### Conservative Treatment

Topical therapies, of which many have been tried, are generally unsuccessful. The only effective nonoperative treatments address the underlying defecation disorder. Patients must learn to avoid straining, to restrict the number of visits to the toilet, and to decrease the duration of each visit. A high-fiber diet may be

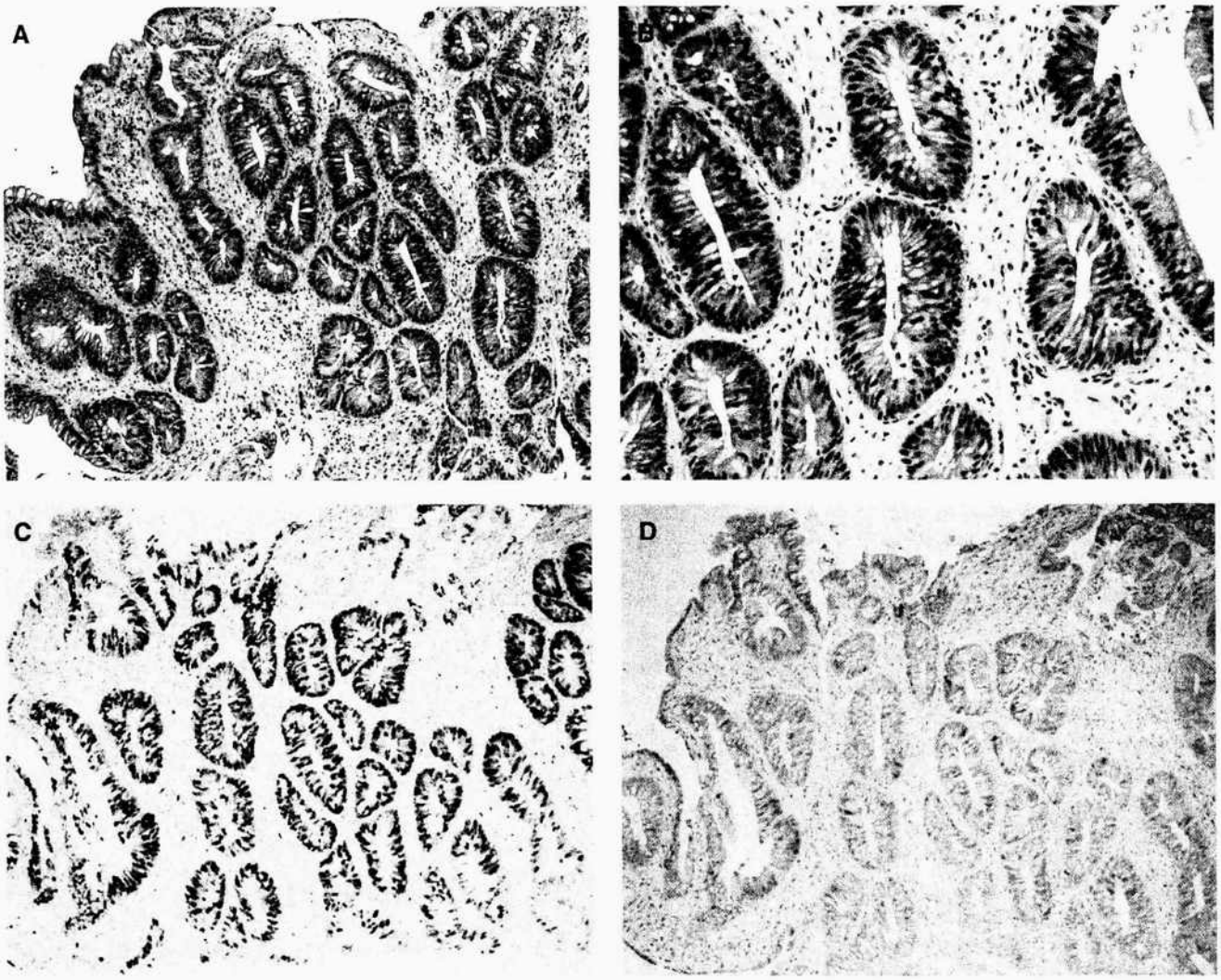


FIGURE 4 (A, B) Marked reactive changes mimicking dysplasia, with stratified nuclei suggesting low-grade dysplasia. (C) Mib-1 (Ki67), a proliferation marker, shows extension of the proliferative zone to the surface. (D) p53 immunostaining is unremarkable, with only occasional nuclei staining in the usual distribution (normal pattern).

helpful. Biofeedback retraining of the defecation mechanism, in combination with patient education, has had variable rates of success, but if the pattern of abnormal defecation can be corrected, most patients will have at least symptomatic improvement if not complete healing of the rectal lesion. The majority of patients can be managed nonoperatively. Biofeedback and counseling may need to be repeated because the benefits appear to deteriorate over time. Biofeedback can be used alone or as an adjunct to operative treatment.

## Operative Treatment

SRUS in association with overt rectal prolapse should be treated by operative repair of the prolapse. Patients with overt rectal prolapse are not helped by nonoperative approaches. The optimal therapeutic approach to occult prolapse is less clear, but if conservative treatment fails, then operative correction of the intussusception is reasonable.

The best way to repair rectal prolapse remains an extremely difficult and contentious issue. Many operations have been described and there is no consensus regarding which is best. It is increasingly accepted that no single operation is best in all circumstances. In selecting the procedure for an individual patient, the surgeon must consider the general health and age of the patient, the morbidity, mortality, and recurrence rate for the operation, and the effect of the operation on concomitant symptoms such as fecal incontinence, constipation, and ineffective emptying. Whatever operative approach is taken, it is essential to recognize that

correction of prolapse is not equivalent to symptom control—fecal incontinence, mucus discharge, tenesmus, and straining may all persist despite control of the prolapse.

The main operative approaches are abdominal and perineal. In general, the abdominal operations have lower recurrence rates compared to the perineal operations, but are associated with greater morbidity, including bleeding, infection, bowel obstruction, and sexual dysfunction secondary to injury of pelvic autonomic nerves. Morbidity may be reduced with a laparoscopic approach.

### *Abdominal Operations*

The medically fit patient has conventionally been treated by an abdominal approach. The popular abdominal operations incorporate fixation of the mobilized rectum to the presacral fascia, with or without resection.

**Rectopexy** The rectum is fully mobilized and as the rectum is retracted in a cephalad direction, the lateral ligaments of the rectum (or lateral rectal tissues) are fixed with sutures to the presacral fascia. The degree to which the rectum should be mobilized anteriorly and laterally is controversial, but there is complete agreement that full posterior mobilization to the tip of the coccyx is important in reducing recurrence. This is a simple procedure with a recurrence rate in the range of 5% in most series. The mobilized rectum may be anchored to the presacral fascia with the use of a prosthetic mesh that partially encircles the rectum. A partial wrap, leaving the anterior one-fourth to one-half of the rectal circumference free, prevents obstruction. The peritoneum is closed over the mesh to avoid adhesion of small bowel loops. The recurrence rate with this approach is also very low, less than 5% in many large series. Unfortunately, rectopexy is often complicated by ongoing problems with evacuation, and this may be especially true in the SRUS population.

**Resection** The resectional procedures are combination rectopexy–resection, anterior resection, and low anterior resection. When resection of the redundant sigmoid colon is added to rectopexy, prosthetic mesh is avoided because of the risk of infection. The colonic resection is generally extended proximally to eliminate the redundant sigmoid colon. Recurrence is in the range of 5–10%. Resection–rectopexy may improve constipation, but the quality of this evidence is poor. Extending the resection below the peritoneal reflection appears to increase morbidity without decreasing the recurrence rate.

**Perineal approaches** The principal attraction of the perineal operations is that they are well tolerated, even by frail patients. The perineal operations can be performed under regional or local anesthesia, and these operations are especially attractive when there has been previous pelvic surgery. As with the abdominal operations, full mechanical and antibiotic bowel preparation is used. The operations may be done in the lithotomy or prone jackknife position.

**Delorme procedure** In this operation, the mucosa is circumferentially stripped off the underlying muscle from 1.5 cm proximal to the dentate line to the tip of the prolapsed rectum; the mucosal tube is dissected until resistance is encountered. The denuded rectal wall is longitudinally plicated with a series of absorbable sutures, the mucosal tube is excised, and the mucosa is reapproximated. The Delorme operation may not be ideal in patients with solitary rectal ulcer syndrome if there is a lot of induration of the rectal wall. Recurrence rates range from 5 to 27%.

**Perineal proctosigmoidectomy** With the rectum prolapsed, a circumferential incision 2 cm proximal to the dentate line is deepened through the full thickness of the bowel wall. The peritoneum is opened and the rectosigmoid is mobilized until the redundant bowel cannot be pulled down any further. Anterior and posterior plication of the levator muscles may be added at this point. About 2 cm distal to the anus, the inner tube of the rectosigmoid is transected along with its mesentery. An anastomosis is performed 1–2 cm proximal to the dentate line. Morbidity and mortality are low, but are probably slightly higher than with the Delorme procedure. Recurrence rates range from 0 to 60%, with most recent reviews reporting recurrence rates of 5–10%.

With all of these operations, healing of the SRUS is expected in the majority of patients; however, long-term symptomatic improvement is only 50–60%. Patients with SRUS who do not have overt prolapse or internal intussusception are not helped by operations. For some patients, a permanent stoma is ultimately established, but even a stoma does not guarantee symptom control.

## SUMMARY

SRUS is an uncommon disorder with distinct clinical, histological, radiographic, and physiologic findings. The pathogenesis is unclear, but probably varies among patients. Correction of an underlying defecation disorder will help many patients. If occult rectal prolapse is present, and if symptoms have persisted after behavior modification, then rectopexy is reasonable. If overt rectal prolapse is present, then this should be repaired.

## See Also the Following Articles

Colitis Cystica Profunda and Solitary Rectal Ulcer Syndrome • Intussusception • Rectal Ulcers

## Further Reading

Felt-Bersma, R. J. F., and Cuesta, M. A. (2001). Rectal prolapse, rectal intussusception, rectocele, and solitary rectal ulcer syndrome. *Gastroenterol. Clin. North Am.* 30(1), 199–222.

Lobert, P. F., and Appelman, H. D. (1981). Inflammatory cloacogenic polyp. A unique inflammatory lesion of the anal transitional zone. *Am. J. Surg. Pathol.* 5(8), 761–766.

Malouf, A. J., Vaizey, C. J., and Kamm, M. A. (2001). Results of behavioral treatment (biofeedback) for solitary rectal ulcer syndrome. *Dis. Colon Rectum* 44, 72–76.

Sitzler, P. J., Kamm, M. A., Nicholls, R. J., and McKee, R. F. (1998). Long-term clinical outcome of surgery for solitary rectal ulcer syndrome. *Br. J. Surg.* 85, 1246–1250.

Tendler, D. A., Aboudola, S., Zacks, J. F., O'Brien, M. J., and Kelly, C. P. (2002). Prolapsing mucosal polyps: An underrecognized form of colonic polyp—A clinicopathological study of 15 cases. *Am. J. Gastroenterol.* 97(2), 370–376.

Tjandra, J. J., Fazio, V. W., Petras, R. E., Lavery, I. C., Oakley, J. R., Milsom, J. W., and Church, J. M. (1993). Clinical and pathologic factors associated with delayed diagnosis in solitary rectal ulcer syndrome. *Dis. Colon Rectum* 36, 146–153.

Vaizey, C. J., Roy, A. J., and Kamm, M. A. (1997). Prospective evaluation of the treatment of solitary rectal ulcer syndrome with biofeedback. *Gut* 41, 817–820.

Vaizey, C. J., van den Bogaerde, J. B., Emmanuel, A. V., Talbot, I. C., Nicholls, R. J., and Kamm, M. A. (1998). Solitary rectal ulcer syndrome. *Br. J. Surg.* 85, 1617–1623.

van Tets, W. F., and Kuijpers, J. H. C. (1995). Internal rectal intussusception—Fact or fancy? *Dis. Colon Rectum* 38, 1080–1083.

# Somatostatin

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**enterochromaffin-like cell** Synthesizes, stores, and secretes histamine as a paracrine regulator in the gastric mucosa.

**gastrin** Gastrointestinal hormone produced by G cells in the gastric antral mucosa; stimulates gastric acid secretion.

**somatostatin** Tetradecapeptide that is an inhibitor of growth hormone release.

**Somatostatin (SST), a tetradecapeptide isolated in the early 1970s from sheep hypothalami, was identified as an inhibitor of growth hormone release. SST has been found in virtually every organ and is recognized as a peptide that exerts an inhibitory action on a variety of physiological functions, acting either as a classical endocrine hormone, a local (paracrine) regulatory factor, or a neurotransmitter. In mammals, the gastrointestinal tract, the brain, and the pancreas contain the highest amounts of SST. In the rat, the gastrointestinal tract accounts for ~65% of the total body SST, the brain for ~25%, the pancreas for ~5%, and the remaining organs for ~5%. In the brain, SST functions as a neurotransmitter, affecting cognitive, locomotor, sensory, and autonomic functions. In the gastrointestinal tract, SST displays a wide array of physiological functions and pharmacological effects, mostly inhibitory, of which the suppression of gastric acid secretion is a landmark response. In view of these properties, different analogues have been developed for the treatment of various human diseases. During the past few years, SST receptor subtypes have been cloned and pharmacologically characterized. Selective SST agonists and antagonists and genetic animal models with selective deletion of receptor subtype have been developed. These new tools are of critical importance to the understanding of SST signaling pathways in the regulation of gastrointestinal function.**

## SOMATOSTATIN GENE AND GENE PRODUCTS

### Somatostatin-14 and -28

In mammals, SST derives from the expression of a single gene that, in humans, maps to the long arm of chromosome 3. The amino acid sequence of SST has

been determined from multiple tissues and has been shown to have remarkable phylogenetic conservation across species. SST is synthesized as prepro-SST and is posttranslationally processed into two different molecular forms, SST-14 and SST-28, with 14 and 28 amino acid residues, respectively. In fish, two separate genes encoding for SST peptides have been identified. One corresponds to the mammalian gene and gives rise only to SST-14. The second generates extended forms of SST, namely, anglerfish-28 (homologue of mammalian SST-28) and catfish-22. The SST-14 sequence is totally conserved, whereas there is only a 40–66% homology between SST-28 and its fish counterparts.

In mammals, SST-28 contains the SST-14 moiety, responsible for the biological activity, at its carboxyl-terminal end. The processing machinery required for the synthesis is present in various tissues with different relative activities. This leads to different tissue-specific types of synthesis and release of SST-14 and -28. SST-14 is the predominant molecular form in the stomach, duodenum, colon, and pancreas. In contrast, in the small intestine, over 50% of the content corresponds to SST-28.

### Cortistatins Are Somatostatin-Like Peptides

A second SST-like gene, called cortistatin, has been cloned in humans and rats. This gene gives rise to two cleavage products—human cortistatin-17 and the rat homologue cortistatin-14, and human and rat cortistatin-29. Unlike the broad tissue expression of the SST gene, expression of the corticostatin gene is restricted to the cerebral cortex.

## TISSUE DISTRIBUTION OF SOMATOSTATIN

SST is distributed throughout the gastrointestinal (GI) tract, being present in specialized endocrine cells and neurons. In mammals, SST is found mainly in the mucosal layer, namely, in endocrine cells termed D cells, which contain 90% of SST in the stomach and duodenum. The remaining SST is present in neuronal structures contributing to both the intrinsic and extrinsic innervation of the gut.

### Endocrine D Cells Are the Main Source of Gastric Somatostatin

In the stomach, D cells are localized both in the antral and the fundic mucosa. These cells have a characteristic morphology, with cytoplasmatic processes that terminate in close proximity to the target cells. Such morphology supports the concept of a paracrine or local regulatory action of SST in the gastric mucosa. In the fundic mucosa, D cells are of a "closed type," without luminal contact, whereas in the antrum they are of an "open type," with their apical membrane exposed to the gastric lumen. This organization correlates with functional responses to different stimuli.

Endocrine D cells can also be found in the intestine and pancreas. Intestinal D cells are flask-shaped cells with their apical membranes open to the lumen, and, therefore, respond to luminal stimuli. In the pancreas, endocrine D cells are a functional component of the islets, participating in the control of the endocrine functions. Table I summarizes the main endocrine sources of gastrointestinal SST in the context of their regulation and biological role.

### Intestinal Somatostatin Is Mainly of Neural Origin

Whereas gastric SST is mainly of endocrine origin, intestinal SST is mainly present in neurons. SST immunoreactivity is detected in the submucosa and muscle layers of the entire gut, with the lowest levels observed in the colon. The majority of the neuronal SST-like immunoreactivity is present in the intrinsic innervation of the gut. For instance, about 20% of the cell bodies in the submucous plexus of the guinea pig small intestine contain SST-like immunoreactivity, corresponding to cholinergic secretomotor neurons. Pancreatic ganglia and nerves also contain significant amounts of SST.

## REGULATION OF SOMATOSTATIN SYNTHESIS AND RELEASE

Anatomical and biochemical studies support the notion that SST is secreted mostly in a paracrine/neurocrine fashion, and therefore circulating levels are relatively low and may not reflect release at local sites. In addition, to avoid spreading of actions, the peptide half-life is relatively short, about 3 minutes in circulation. All these factors make it difficult to study SST release and regulation *in vivo*. Consequently, isolated preparations have been widely used to assess SST release.

### Intraluminal Stimuli Influence Gastric Somatostatin Release

Intraluminal factors associated with the diet, food components, and low pH are the main stimulants of SST release from open-type endocrine D cells in the stomach and intestine. For instance, luminal acid is the main stimulant of gastric SST release from antral D cells.

TABLE I Sources and Biological Actions of SST of Endocrine Origin in the Gastrointestinal Tract[a]

| Localization | Cellular type | Releasing stimuli | Targets | Biological actions | Mechanism of action |
|---|---|---|---|---|---|
| Fundic mucosa | Closed | Neural input (ACh, GRP), endocrine (gastrin, CCK) | ECL cells, parietal cells | Inhibition of histamine release, direct inhibition of secretion | Paracrine |
| Antral mucosa | Open | Luminal (nutrients, pH), sensory neurons | G cells | Inhibition of gastrin synthesis and release | Paracrine |
| Intestinal epithelium | Flasklike, open | Luminal (nutrients) | Various cell types | Inhibition of neuroendocrine secretion, modulation of motility, inhibition of intestinal transport, inhibition of splanchnic blood flow, inhibition of tissue growth/proliferation, modulation of food intake | Paracrine Endocrine Neurocrine |
| Pancreatic islets | Closed | Endocrine, circulating nutrients (glucose) | Other islet cell types | Inhibition of insulin and glucagon release | Neurocrine Endocrine |

[a] Abbreviations: ACh, acetylcholine; GRP, gastrin-releasing peptide; CCK, cholecystokinin; ECL, enterochromaffin-like.

Similarly, the presence of nutrients and acid in the duodenum stimulates the release of gastric SST, an effect probably mediated through the release of intestinal enterogastrones. SST release through these mechanisms is of physiological importance for the feedback regulation of gastric acid secretion. Physiological postprandial changes of SST levels in the peripheral circulation or portal blood originate from gastric and intestinal SST release. Other sources do not contribute to the peripheral plasma SST levels.

### The Autonomic Nervous System Differentially Affects Somatostatin Release

The autonomic nervous system also exerts an important role in the regulation of SST release from the gut. As in other systems, the sympathetic and parasympathetic components have opposite effects on SST release. Adrenergic agonists, acting through β-adrenergic receptors, stimulate gastric SST release. In contrast, muscarinic cholinergic agents inhibit SST release. However, the existence of vagal nonadrenergic stimulatory pathways for SST release has also been described in some species. These actions explain, at least in part, the inhibitory and stimulatory effects that the sympathetic and parasympathetic nervous systems have, respectively, on acid secretion.

### Gut Peptides Modulate Somatostatin Release

In addition to the luminal and autonomic control, several regulatory peptides, acting as classical hormones or as neuropeptides, modulate gastrointestinal SST release. These can be categorized as stimulatory and inhibitory agents. The most important stimulants of SST release are gastrin and cholecystokinin (CCK). Other peptides, such as peptides of the secretin family, bombesin/gastrin-releasing peptide (GRP), glucose-dependent insulinotropic peptide, oxyntomodulin, or glucagon-like peptide-1 (GLP-1), which consistently inhibit gastric acid secretion, may function by stimulating SST release. On the other hand, substance P, opioids, insulin, and glucagon are potent inhibitors of SST release. In addition, *in vitro* studies suggest that fundic D cells are under negative feedback control by their own product through an autocrine mechanism of action. However, so far, no SST receptors have been localized on D cells.

## SOMATOSTATIN RECEPTORS

SST acts on its target cells through high-affinity plasma membrane receptors (Table II). To date, five different SST receptor (SSTR) subtypes, SSTR1–5, belonging to the superfamily of G protein-coupled receptors with seven transmembrane domains, have been cloned and pharmacologically characterized in different systems. In addition, two splice variants of SSTR2, SSTR2a and SSTR2b, which differ in length and composition of their intracellular carboxy termini, have been isolated and cloned in the mouse and the rat. Overall, there is a 39–57% sequence identity among the different receptor subtypes. The five receptors also have a remarkable degree of structural

**TABLE II Characteristics of the Cloned Human SST Receptor Subtypes**

| Characteristic[a] | SSTR1 | SSTR2a | SSTR3 | SSTR4 | SSTR5 |
|---|---|---|---|---|---|
| Chromosomal localization | 14q13 | 17q24 | 22q13.1 | 20p11.2 | 16p13.3 |
| Amino acids | 391 | 369 | 418 | 388 | 363 |
| G protein coupling | + | + | + | + | + |
| Effector coupling | | | | | |
| Adenylyl cyclase | ↓ | ↓ | ↓ | ↓ | ↓ |
| Tyrosine phosphatase | ↑ | ↑ | ↑ | ↑ | ↑ |
| MAP kinase | ↑ | ↓ | ↓↑ | ↑ | ↓ |
| $K^+$ channels | | ↑ | ↑ | ↑ | ↑ |
| $Ca^{2+}$ channels | ↓ | ↓ | | | |
| $Na^+/H^+$ exchanger | ↑ | | | | |
| AMPA/kainate glutamate channels | ↑ | ↓ | | | |
| Phospholipase $C/IP_3$ | | ↑ | | | ↓↑ |
| Phospholipase A2 | | | | ↑ | |
| Tissue distribution | Brain, pituitary, GI tract, kidney | Brain, pituitary, GI tract, kidney | Brain, pituitary, GI tract, kidney | Brain, pituitary, GI tract, lungs, placenta | Brain, pituitary, GI tract |

[a] Abbreviations: MAP, mitogen-activated protein; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid.

conservation across species, with between 80 and 99% homology among the human, rat, and mouse isoforms. The nearest relatives of SST receptors are the opioid receptors that share about 37% sequence similarity to the mouse SSTR1.

Early studies, based on receptor autoradiography using nonselective ligands, showed a high density of SST binding sites all along the GI mucosa as well as in neural structures. In recent years, the anatomical and cellular distribution of SST receptor gene expression has been established in rodent and human tissues as well as in different tumors and cell lines. Lately, the development of SST receptor subtype-selective antibodies has allowed the direct localization of the SST receptor at the protein level by immunohistochemistry. These studies reveal an intricate pattern of receptor expression throughout the central nervous system and the periphery, with an overlapping but characteristic pattern that is receptor subtype selective and tissue and species specific.

## G Protein Coupling and Signal Transduction of Somatostatin Receptors

The activation of SST receptors by SST ligands elicits cellular responses through G protein-linked modulation of multiple second-messenger systems, including adenylyl cyclase, $Ca^{2+}$ and $K^+$ ion channels, the $Na^+/H^+$ antiporter, guanylate cyclase, phospholipase C, phospholipase A2, mitogen-activated protein (MAP) kinase, and serine, threonine, and phosphotyrosyl protein phosphatase. These pathways show only partial receptor selectivity (Table II). In general, all five receptor subtypes, and especially the human isoforms, are potent inhibitors of adenylyl cyclase and cyclic adenosine monophosphate (cAMP) formation via pertussis toxin-sensitive G proteins. Subtypes 1, 2, 3, and 5 display acute desensitization of adenylyl cyclase coupling.

In the presence of the agonist, receptor subtypes 2, 3, 4, and 5 undergo rapid internalization. Receptor subtype 1 fails to be internalized but is instead up-regulated at the membrane in response to continued agonist exposure.

## The SSTR2 Is the Receptor Subtype Predominant in the Stomach

The presence of the five SST receptor subtypes in the stomach, with a predominance of SSTR2 receptor mRNA, has been established by ribonuclease protection assays and reverse transcription polymerase chain reaction (RT-PCR). At a cellular level, *in situ* hybridization studies demonstrate the presence of SSTR2 mRNA-containing cells in the gastric mucosa and submucosa as well as in the myenteric plexus and the external muscle layer. In addition, RT-PCR techniques show that the mRNAs for both SSTR2a and SSTR2b isoforms are present in the stomach. Immunohistochemical studies using antipeptide antibodies specific for the SSTR2a and SSTR2b receptors show that a small population of enterochromaffin-like (ECL) cells in the stomach expresses SSTR2a receptors. On the other hand, the SSTR2b receptor is mainly localized in parietal cells and in high concentration in ECL cells. So far, no SST receptors have been found in other cellular types of the gastric mucosa.

SSTR2a has also been localized in nerve fibers that arise from the nervous plexuses and innervate the mucosa with fibers running parallel to the epithelia. Many of these fibers are in close proximity to D cells of the gastric mucosa. This distribution strongly suggests that SSTR2a receptors might mediate SST effects in the GI tract via neuronal and paracrine pathways.

### All SSTR Receptor Subtypes Are Present in the Intestine

*In situ* hybridization studies have identified all five receptor subtypes in the rat duodenum, jejunum, ileum, and colon. All receptor subtypes are present in the epithelium, submucosal plexus, and muscle layers, whereas only SSTR1–3 are found in the myenteric plexus. Immunohistochemical studies have demonstrated the existence of SSTR2a receptors in the myenteric and submucosal plexuses, with a predominance in the submucosal plexus, and in fibers innervating the muscle, mucosa, and vasculature. The SSTR2a receptors are present in the neuronal soma and processes as well as in axon terminals, suggesting both pre- and postsynaptic effects of SST in the gut. Moreover, this distribution is consistent with SSTR2a receptors being expressed by functionally distinct enteric neurons, indicating that SST plays a significant role in the regulation of intestinal motor and secretory functions. In addition, SSTR2a receptors are present in interstitial cells of Cajal, indicative of other target cells for SST to regulate smooth muscle activity.

### SSTR2 and SSTR5 Are the Main Receptor Subtypes in the Pancreas

Early autoradiographic studies established the presence of SST binding sites in alpha and beta cells from pancreatic islets. Molecular studies have shown that rat islets contain mRNA for all five receptor subtypes, although this does not imply the presence of functional receptors. In humans, immunohistochemical studies have revealed a predominant expression of SSTR2 and SSTR5, with a specific cellular distribution: beta cells are rich in SSTR5, alpha cells contain mostly SSTR2, and delta cells contain SSTR5.

### Neuroendocrine Enteropancreatic Tumors Express Somatostatin Receptors

In addition to normal tissues, the majority of human tumors, either benign or malignant, express high concentrations of SST receptors, frequently featuring more than one isotype. SST receptors are especially present in almost all neuroendocrine enteropancreatic tumors [gastrinoma, vasoactive intestinal peptide-producing tumor (VIPoma), carcinoid, insulinoma, glucagonoma, SSToma, pancreatic polypeptide-producing tumor (PPoma), and growth hormone releasing factor-producing tumor (GRFoma)]. The expression appears to be tumor specific, but in general the pattern is SSTR2 > SSTR1 > SSTR3 > SSTR4 > SSTR5. However, studies carried out so far are mainly based on mRNA expression, which may not necessarily reflect functional receptor levels. SSTR2 predominance is found in about 90% of carcinoid tumors and 80% of endocrine pancreatic tumors.

## BIOLOGICAL ACTIONS OF SOMATOSTATIN IN THE GASTROINTESTINAL TRACT: RECEPTOR SUBTYPE SELECTIVITY

### Somatostatin Is the Main Inhibitor of Gastric Acid Secretion

SST is a potent inhibitor of gastric acid secretion and probably the main inhibitory regulator during the cephalic, gastric, and intestinal phases of secretion. SST administered peripherally inhibits gastric acid secretion at doses producing plasma increments of the peptide similar to those observed during postprandial states in dogs and humans. The SST-dependent regulation of gastric acid secretion involves gastric SST produced by fundic and antral endocrine D cells, acting locally through paracrine, rather than endocrine, mechanisms. Fundic D cells are stimulated by gastrin and by acetylcholine, as well as by other neuropeptides; they are closely associated to parietal cells and ECL cells through cytoplasmic extensions. Antral D cells respond to changes in gastric luminal acidity and are closely associated, by way of cytoplasmic extensions, with their target cells, i.e., G cells, resulting in the local release of SST, which, in turn, inhibits gastrin synthesis and release from G cells.

During both the cephalic and gastric phases of a meal, gastric acid secretion is stimulated mainly through the release of gastrin. Attenuation of excessive acid secretion can be attributed to the local release of SST, which, in turn, regulates the activity of G cells, ECL cells, and parietal cells. Physiological effects of SST result from a direct inhibition of parietal cell secretion and indirectly by inhibition of histamine release from ECL cells and gastrin release from G cells. The role of SST in the control of basal (interdigestive) gastric acid secretion is less clear. *In vitro* studies suggest that SST

tonically inhibits acid secretion; however, this has not been fully demonstrated in *in vivo* conditions.

### *SSTR2 Receptors Mediate the Effects of Somatostatin on Gastric Acid Secretion*

Several *in vivo* and *in vitro* studies in rats, mice, dogs, and humans using different relatively selective receptor peptide analogues of SST have established that the SSTR2 receptor subtype mediates the inhibitory effects of SST on gastric acid secretion (Table III). Further functional evidence for the involvement of SSTR2 receptors on SST-dependent control of gastric acid secretion comes from the use of the selective SSTR2 antagonist PRL-2903. Infused intravenously, PRL-2903 antagonizes SST-induced inhibition of acid secretion. Conclusive evidence for the involvement of SSTR2 receptors in the regulation of gastric acid secretion also comes from functional studies in mice with targeted disruption of the SSTR2a receptor gene. Because the SSTR2b variant is a spliced product of the SSTR2a variant, these animals lack both forms of the receptor, therefore none of the splice variants is expressed and no information regarding the SSTR2 isoform mediating SST actions on acid secretion can be derived.

### *SSTR2 Receptors Mediate Somatostatin-Dependent Inhibition of Gastrin and Histamine Release*

SST-induced inhibition of gastrin and histamine secretion is also mediated by the activation of SSTR2 receptors located, respectively, in G cells and ECL cells. Effects on gastrin release are further supported by studies with the SSTR2 antagonist, PRL-2903, showing that the antagonist increases plasma levels of gastrin.

### *D Cells as an Integrator of Inhibitory Responses in the Stomach*

Several gut peptides [i.e., amylin, adrenomedullin, calcitonin gene-related peptide (CGRP), bombesin, glucose-dependent insulinotropic polypeptide, GLP-1, or pituitary adenylate cyclase-activating polypeptide (PACAP)] inhibit gastric acid secretion through the release of SST or have SST-dependent mechanisms of action. In addition, receptors for several of these neuropeptides have been localized in gastric D cells. These functional and morphological observations suggest that gastric D cells may function as a common target for a variety of gut peptides. Activation of D cell by these peptides translates into the release of SST, and in turn the activation of SSTR2 receptors on ECL and parietal cells leading to an inhibition of acid output.

## Somatostatin and Small Intestinal Function

SST inhibits small bowel motility and intestinal absorption of nutrients. In the small intestine, neuronal SST is released locally by intestinal distension and participates, as a neuromodulator, in the coordination of the descending relaxation of the peristaltic reflex. Pharmacological studies and the use of SSTR2 knockout mice have indicated that this receptor subtype is involved in peristalsis, however the implication of other receptor subtypes cannot be ruled out.

## Somatostatin Regulates Pancreatic Function through SSTR2 and SSTR5 Receptors

SST affects both exocrine and endocrine pancreatic secretion, acting through paracrine and endocrine mechanisms. Pharmacological studies in normal and SSTR2 knockout mice have shown that pancreatic actions of SST are mediated mainly through SSTR2 and SSTR5 receptors.

### *Somatostatin Inhibits Pancreatic Amylase Release through SSTR5 Receptors*

Modulation of exocrine pancreatic function is associated with changes in arterial SST of gastric or intestinal origin (endocrine action). Physiological changes in plasma SST levels inhibit pancreatic enzyme and bicarbonate secretion. Pharmacological studies using receptor-selective analogues of SST have identified the SSTR5 as the main receptor subtype inhibiting amylase release.

TABLE III Receptor Selectivity of SST Actions in the Gastrointestinal Tract

| Biological activity | Receptor subtype | Localization |
|---|---|---|
| Inhibition of gastric acid secretion | SSTR2 | Parietal cells |
| Inhibition of histamine release | SSTR2 | Enterochromaffin-like cells |
| Modulation of the peristaltic reflex | SSTR2/other undetermined | Myenteric plexus |
| Inhibition of pancreatic amylase release | SSTR5 | Acinar cells |
| Inhibition of insulin release | SSTR5 | Pancreatic beta cells |
| Inhibition of glucagon release | SSTR2 | Pancreatic alpha cells |
| Inhibition of cell proliferation | SSTR1, 2, 3, 4, and 5 | Tumor cells |

Supporting this observation, binding studies have also identified the presence of SSTR5 receptors on pancreatic acinar cells.

### *Somatostatin Inhibits Pancreatic Endocrine Secretion through SSTR2 and SSTR5 Receptors*

SST from D cells in the pancreatic islets acts locally (paracrine) on alpha, beta, and PP cells, inhibiting the release of glucagons, insulin, and PP, respectively. This interaction provides a basic intraislet control of insulin release. Pharmacological studies using receptor-selective analogues of SST in normal and SSTR2 and SSTR5 knockout mice have shown that islet regulation is receptor and hormone specific. Stimulation of SSTR5 receptors located on beta cells is the main pathway to inhibit insulin secretion, whereas the inhibition of glucagon release from alpha cells depends on the stimulation of SSTR2 receptors.

## PATHOPHYSIOLOGICAL ASPECTS OF SST

A clear pathophysiological role of SST has been demonstrated only in cases with SST-producing tumors (SSTomas). In these patients, the clinical signs are associated with an overproduction and high levels of plasma SST. The resulting syndrome is characterized by diabetes, gallstones, malabsorption, and pancreatic insufficiency.

Alterations in the responsiveness and number of gastric D cells might be related to the hypersecretory states observed in patients with nonatrophic gastritis associated with *Helicobacter pylori* infection and in patients with duodenal or gastric ulcers. Under these conditions, D cell responsiveness to gastrin and other stimulants will be reduced. This will lead to lower levels of SST, which, in turn, results in an increased gastrin release and gastric acid output. However, although these mechanisms have been established in several animal models, their importance for human pathophysiology remains to be elucidated.

## THERAPEUTIC USE OF SST IN GASTROENTEROLOGICAL DISORDERS

SST and its stable analogue octreotide have been consistently used in the treatment of esophageal variceal bleeding, pathological states of the exocrine pancreas, and neuroendocrine enteropancreatic tumors. Gut neuroendocrine tumors contain abundant SST receptors, and this has been used as a diagnostic tool for tumor localization. In addition, receptors have been demonstrated to be functional in most cases and either SST or its analogue, octreotide, has been used as symptomatic therapy. The mechanisms for the symptomatic improvement are due to SSTR-mediated inhibition of mediators release that leads to the major associated symptoms. In addition, SST and octreotide seem to have an inhibitory effect on cell growth and proliferation, reducing tumor size. So far, all receptor subtypes have been shown to induce cell cycle arrest in different tumor cell lines, although through different mechanisms (Table III).

SST and the analogue octreotide reduce intestinal secretion and have been used to treat diarrhea. SST was originally shown to be effective in treating diarrhea caused by neuroendocrine tumors that produced VIP (VIPoma). In this condition, SST reduced both the production of VIP and its effects on the intestine. It has since been recognized that SST analogues are also effective in treating other diarrheal conditions.

## See Also the Following Articles

**Anti-Diarrheal Drugs • Cholecystokinin (CCK) • Gastric Acid Secretion • Gastrin • Growth Hormone • Histamine • Pancreatic Enzyme Secretion (Physiology) • Portal Hypertension and Esophageal Varices • Variceal Bleeding • Vasoactive Intestinal Peptide (VIP)**

## Further Reading

Abdu, F., Hicks, G. A., Hennig, G., Allen, J. P., and Grundy, D. (2002). Somatostatin sst2 receptors inhibit peristalsis in the rat and mouse jejunum. *Am. J. Physiol.* 282, G624–G633.

Arnold, R., Wied, M., and Behr, T. H. (2002). Somatostatin analogues in the treatment of endocrine tumors of the gastrointestinal tract. *Expert Opin. Pharmacother.* 3, 643–656.

Chiba, T., and Yamada, T. (1994). Gut somatostatin. *In* "Gut Peptides" (J. H. Walsh and G. J. Dockray, eds.), pp. 123–145. Raven Press, New York.

Hofland, L. J., and Lamberts, S. W. (2001). Somatostatin receptor subtype expression in human tumors. *Ann. Oncol.* 12(Suppl. 2), S31–S36.

Lloyd, K. C. K., and Walsh, J. (1994). Gastric secretion. *In* "Gut Peptides" (J. H. Walsh and G. J. Dockray, eds.), pp. 633–645. Raven Press, New York.

Martinez, V. (2002). Somatostatin receptors and the control of gastric acid secretion. *In* "Gut–Brain Peptides in the New Millennium" (Y. Taché, Y. Goto, G. Ohning, and T. Yamada, eds.), pp. 167–178. CURE Foundation, Los Angeles.

Martinez, V., Curi, A. P., Torkian, B., Schaeffer, J. M., Wilkinson, H. A., Walsh, J. H., and Taché, Y. (1998). High basal gastric acid secretion in somatostatin receptor subtype 2 knockout mice. *Gastroenterology* 114, 1125–1132.

Patel, Y. C. (1999). Somatostatin and its receptor family. *Front. Neuroendocrinol.* 20, 157–198.

Piqueras, L., Taché, Y., and Martinez, V. (2003). Somatostatin receptor type 2 mediates bombesin-induced inhibition of gastric acid secretion in mice. *J. Physiol. (Lond.)* (in press).

Schusdziarra, V. (1996). Somatostatin: Biological actions and pathophysiology. *In* "Octreotide: From Basic Science to Clinical Medicine" (C. Scarpignato, ed.), pp. 35–53. Karger, Basel.

Sternini, C., Wong, H., Wu, S. V., de Giorgio, R., Yang, M., Reeve, J., Jr., Brecha, N. C., and Walsh, J. H. (1997). Somatostatin 2A receptor is expressed by enteric neurons, and by interstitial cells of Cajal and enterochromaffin-like cells of the gastrointestinal tract. *J. Comp. Neurol.* 386, 396–408.

Strowski, M. Z., Kohler, M., Chen, H. Y., Trumbauer, M. E., Li, Z., Szalkowski, D., Gopal-Truter, S., Fisher, J. K., Schaeffer, J. M., Blake A. D., Zhang, B. B., and Wilkinson, H. A. (2003). Somatostatin receptor subtype 5 regulates insulin secretion and glucose homeostasis. *Mol. Endocrinol.* 17, 93–106.

Strowski, M. Z., Parmar, R. M., Blake, A. D., and Schaeffer, J. M. (2000). Somatostatin inhibits insulin and glucagon secretion via two receptor subtypes: An *in vitro* study of pancreatic islets from somatostatin receptor 2 knockout mice. *Endocrinology* 141, 111–117.

Vuyyuru, L., Harrington, L., Arimura, A. S., and Schubert, M. L. (1997). Reciprocal inhibitory paracrine pathways link histamine and somatostatin secretion in the fundus of the stomach. *Am. J. Physiol.* 273, G106–G111.

# Sphincter of Oddi Dysfunction

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**ampullary stenosis** Narrowing of the ampulla, often causing obstruction.

**botulinum toxin** Protein produced by *Clostridium botulinum* bacteria, used therapeutically to paralyze or weaken the muscle into which it is injected.

**endoscopic retrograde cholangiopancreaticography** Fiber-optic endoscope insertion into the duodenum and dye injection via the ampulla of Vater, to visualize the biliary and pancreatic ducts.

**endoscopic sphincterotomy** Cutting of the sphincter via an endoscopic approach.

**postcholecystectomy pain** Painful attacks that occur after removal of the gallbladder.

**quantitative hepatobiliary scintigraphy** Nuclear medicine study that assesses bile flow through the biliary tract.

**recurrent pancreatitis** Recurrent inflammation of the pancreas.

**Rome II criteria** Consensus criteria developed to diagnose sphincter of Oddi dysfunction.

**sphincter ablation** Surgical removal of the sphincter.

**sphincter of Oddi dysfunction** Abnormality in the contractility of the sphincter of Oddi.

**sphincter of Oddi manometry** Manometric studies of the sphincter of Oddi.

**Since its original description by Rugero Oddi in 1887, the sphincter of Oddi has been the subject of much study and controversy. Its very existence as a distinct anatomic or physiologic entity has been disputed. Hence, it is not surprising that the clinical syndrome of sphincter of Oddi dysfunction and its therapy are controversial areas. Nevertheless, this dysfunction is commonly diagnosed and treated by physicians, requiring both knowledge of the anatomy and physiology of the sphincter of Oddi and clinical presentations and methods to diagnose and treat sphincter of Oddi dysfunction.**

## DEFINITIONS

Sphincter of Oddi dysfunction (SOD) refers to an abnormality of sphincter of Oddi contractility. Dysfunction manifests as a benign, noncalculous obstruction to flow of bile or pancreatic juice through the pancreaticobiliary junction, i.e., the sphincter of Oddi (SO). SOD may be manifested clinically by pancreaticobiliary pain, pancreatitis, or deranged liver function tests. The dysfunction is actually made up of two entities. SO dyskinesia refers to a primary motor abnormality of the SO that may result in a hypotonic sphincter but more commonly is seen as a hypertonic sphincter. In contrast, SO stenosis refers to a structural alteration of the sphincter, probably from an inflammatory process with subsequent fibrosis. Because it is often impossible to distinguish patients with SO dyskinesia from those with SO stenosis, the diagnosis "sphincter of Oddi

TABLE I Hogan–Geenen Sphincter of Oddi Classification System Related to the Frequency of Abnormal Sphincter of Oddi Manometry and Pain Relief by Biliary Sphincterotomy

| Patient group classification | | Approximate frequency of abnormal sphincter manometry | Probability of pain relief by sphincterotomy if manometry is | | Manometry before sphincter ablation |
|---|---|---|---|---|---|
| Type | Description | | Abnormal | Normal | |
| Biliary I | Patients with biliary-type pain, abnormal aspartate transaminase or alkaline phosphatase > twice normal, documented on two or more occasions, delayed drainage of ERCP contrast from the biliary tree >45 minutes, and dilated common bile duct > 12 mm in diameter | 75–95% | 90–95% | 90–95% | Unnecessary |
| Biliary II | Patients with biliary-type pain but only one or two of the above criteria | 55–65% | 85% | 35% | Highly recommended |
| Biliary III | Patients with only biliary-type pain and no other abnormalities | 25–60% | 55–65% | <10% | Mandatory |

dysfunction" has been generally applied to both groups of patients. In an attempt to deal with this overlap in etiology, and also to determine the appropriate utilization of SO manometry (SOM), the Hogan–Geenen clinical SOD classification system has been developed for patients with suspected SOD (Table I); this classification is based on clinical history, laboratory results, and endoscopic retrograde cholangiopancreaticography (ERCP) findings.

A variety of less accurate clinical and diagnostic terms are sometimes used in the medical literature to describe SOD, including papillary stenosis, ampullary stenosis, biliary dyskinesia, and postcholecystectomy syndrome (even though SOD may occur with the gallbladder intact).

## ANATOMY, PHYSIOLOGY, AND PATHOPHYSIOLOGY

The sphincter of Oddi is a small complex of smooth muscles surrounding the terminal common bile duct, main (ventral) pancreatic duct (of Wirsung), and the common channel (ampulla of Vater), when present. It has both circular and "figure-eight" components. The high-pressure zone generated by the sphincter is variably 4–10 mm. in length. Its role is to regulate bile and pancreatic exocrine juice flow and to prevent duodenum-to-duct reflux (i.e., to maintain a sterile intraductal environment). The SO possesses both a variable basal pressure and phasic contractile activity. The former appears to be the predominant mechanism, regulating outflow of pancreaticobiliary secretion into the intestine. Although phasic SO contractions may aid in regulating bile and pancreatic juice flow, their primary role appears to be maintaining a sterile intraductal milieu. Sphincter regulation is under both neural and hormonal control. Phasic wave activity of the sphincter is closely tied to the migrating motor complex (MMC) of the duodenum. Innervation of the bile duct does not appear to be essential, based on reports that sphincter function is preserved following liver transplantation. Although regulatory processes vary among species, cholecystokinin and secretin appear to be most important in causing sphincter relaxation, whereas nonadrenergic, noncholinergic neurons, which at least in part transmit vasoactive intestinal peptide (VIP) and nitric oxide, also relax the sphincter. The role of cholecystectomy in altering these neural pathways needs further definition. Luman and colleagues reported that cholecystectomy, at least in the short-term, suppresses the normal inhibitory effect of pharmacological doses of cholecystokinin (CCK) on the sphincter of Oddi. However, the mechanism of this effect is unknown.

Wedge specimens of the SO obtained at surgical sphincteroplasty from patients with SOD show evidence of inflammation, muscular hypertrophy, fibrosis, or adenomyosis within the papillary zone in approximately 60% of patients. In the remaining 40% of patients with normal histology, a motor disorder is suggested.

Less commonly, infections with cytomegalovirus or *Cryptosporidium*, as may occur in AIDS patients, or *Strongyloides* have caused SOD.

How does SOD cause pain? From a theoretical point of view, abnormalities of the SO can give rise to pain by impeding the flow of bile and pancreatic juice, resulting in ductal hypertension, ischemia arising from spastic contractions, and "hypersensitivity" of the papilla. Although unproved, these mechanisms may act alone or in concert to explain the genesis of pain.

## EPIDEMIOLOGY

SOD may occur in pediatric or adult patients of any age; however, patients with SOD are typically middle-aged females. A survey on functional gastrointestinal disorders confirmed that SOD affects females more frequently than males and indicated a high association with work absenteeism, disability, and health care use. Although SOD most commonly occurs after cholecystectomy, it may be present with the gallbladder *in situ*.

Postcholecystectomy pain resembling the patient's preoperative biliary colic occurs in at least 10–20% of patients. The frequency of diagnosing SOD in reported series varies considerably with the patient selection criteria, the definition of SOD utilized, and the diagnostic tools employed. In a British report, sphincter of Oddi dysfunction was diagnosed in 9% of 451 consecutive patients being evaluated for postcholecystectomy pain. Roberts-Thomson evaluated 431 similar patients and found SOD in 11%. In a subpopulation of such patients with a normal ERCP (except dilated ducts in 28%) and recurrent pain of more than 3 months' duration, SOD was diagnosed in 68%. Sherman and colleagues used SOM to evaluate 115 patients with pancreaticobiliary pain with and without liver function test abnormalities. Patients with bile duct stones and tumors were excluded from analysis. Fifty-nine of 115 patients (51%) had an abnormal basal sphincter of Oddi pressure greater than 40 mmHg. These patients were further categorized by the Hogan–Geenen SOD classification system (Table 1). The frequency of abnormal manometry was 86, 55, and 28%, for types I, II, and III patients, respectively. These abnormal manometric frequencies are very similar to those reported by others for type I and type II patients. In type III patients, the finding of an abnormal basal sphincter pressure has varied from 12 to 55%. As noted, patient selection factors may be one explanation for this great variability.

SOD can involve abnormalities in either the biliary sphincter, pancreatic sphincter, or both. The true frequency of SOD would then depend on whether one or both sphincters were studied. To fully assess the sphincter by SOM, both the bile duct and pancreatic ducts must be evaluated. In a series of 360 patients with pancreaticobiliary pain, 19% had abnormal pancreatic sphincter basal pressure alone, 11% had abnormal biliary basal sphincter pressure alone, and in 31%, the basal pressure was abnormal for both sphincters (overall frequency of SOD was 61%). Dysfunction may occur in the pancreatic duct portion of the SO and cause recurrent pancreatitis and pancreatic-type pain. Although a pancreatic SOD classification system has been developed (similar to the biliary SOD classification system), it has not been widely utilized. Manometrically documented SOD has been reported in 15–72% of patients with recurrent pancreatitis, previously labeled as idiopathic.

## CLINICAL PRESENTATION

Abdominal pain is the most common presenting symptom of patients with SOD. The pain is usually epigastric or right upper quadrant, may be disabling, and lasts for 30 minutes to several hours. In some patients, the pain is continuous with episodic exacerbations. It may radiate to the back or shoulder and be accompanied by nausea and vomiting. Food or narcotics may precipitate the pain. The pain may begin several years after a cholecystectomy was performed for a gallbladder dysmotility or stone disease and is similar in character to the pain leading to the cholecystectomy. Alternatively, patients may have continued pain that was not relieved by a cholecystectomy. Jaundice, fever, or chills are rarely observed. The Rome II diagnostic criteria for SOD are episodes of severe steady pain located in the epigastrium and right upper quadrant, and all of the following criteria: (1) symptom episodes last 30 minutes or more with pain-free intervals, (2) symptoms have occurred on one or more occasions in the previous 12 months, (3) the pain is steady and interrupts daily activities or requires consultation with a physician, and (4) there is no evidence of structural abnormalities to explain the symptoms. The pain is not relieved by trial medications for acid–peptic disease or irritable bowel syndrome. Laboratory abnormalities consisting of transient elevation of liver function tests, typically during episodes of pain, are present in less than 50% of patients. After initial evaluation, patients are commonly categorized according to the Hogan–Geenen SOD classification system (Table 1). Patients with SOD may present with typical pancreatic pain (epigastric and/or left upper quadrant radiating to the back) and recurrent pancreatitis.

### Clinical Evaluation

The diagnostic approach to suspected SOD may be influenced by the presence of key clinical features.

However, the clinical manifestations of functional abnormalities of the SO may not always be easily distinguishable from those caused by organic ones (e.g., common bile duct stones) or other functional nonpancreaticobiliary disorders (e.g., irritable bowel syndrome).

### General Initial Evaluation

Evaluation of patients with suspected SOD (i.e., patients with upper abdominal pain with characteristics suggestive of a pancreatobiliary origin) should be initiated with standard serum liver chemistries, serum amylase and/or lipase, abdominal ultrasonography, and/or computed tomography (CT) scans. The serum enzyme studies should be drawn during bouts of pain, if possible. Mild elevations (less than twice the upper limits of normal) are frequent in SOD, whereas greater abnormalities are more suggestive of stones, tumors, and liver parenchymal disease. Although the diagnostic sensitivity and specificity of abnormal serum liver chemistries are relatively low, recent evidence indicates that the finding of abnormal liver tests in biliary type II patients may predict a favorable response to endoscopic sphincterotomy. CT scans and abdominal ultrasounds are usually normal but occasionally a dilated bile duct or pancreatic duct may be found (particularly in patients with type I SOD). Standard evaluation and treatment of other more common upper gastrointestinal conditions, such as peptic ulcer disease and gastroesophageal reflux, should be done simultaneously. In the absence of mass lesions, stones, or response to acid-suppression therapeutic trials, the suspicion for sphincter disease is heightened.

## DIAGNOSTIC METHODS (NONINVASIVE)

Because SOM (considered by most authorities to be the gold standard for diagnosing SOD) is difficult to perform, invasive, not widely available, and associated with a relatively high complication rate, several noninvasive and provocative tests have been designed in an attempt to identify patients with SOD.

### Morphine–Prostigmin Provocative Test (Nardi Test)

Morphine has been shown to cause sphincter of Oddi contraction. Prostigmin (neostigmine), 1 mg subcutaneously, is added as a vigorous cholinergic secretory stimulant to morphine (10 mg subcutaneously) to make this challenge test. The morphine–Prostigmin test, historically, had been used extensively to diagnose SOD. Reproduction of the patient's typical pain associated with a fourfold increase in aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase, amylase, or lipase constitutes a positive response. The usefulness of this test is limited by its low sensitivity and specificity in predicting the presence of SOD and its poor correlation with outcome after sphincter ablation. This test has largely been replaced by tests believed to be more sensitive.

### Ultrasonographic Assessment of Extrahepatic Bile Duct and Main Pancreatic Duct Diameter after Secretory Stimulation

After a lipid-rich meal or cholecystokinin administration, the gallbladder contracts, bile flow from the hepatocytes increases, and the sphincter of Oddi relaxes, resulting in bile entry into the duodenum. Similarly, after a lipid-rich meal or secretin administration, pancreatic exocrine juice flow is stimulated and the sphincter of Oddi relaxes. If the sphincter of Oddi is dysfunctional and causes obstruction to flow, the common bile duct or main pancreatic duct may dilate under secretory pressure. This can be monitored by transcutaneous ultrasonography. Sphincter and terminal duct obstruction from other causes (stones, tumors, strictures, etc.) may similarly cause ductal dilation and need to be excluded. Pain provocation should also be noted if present. To date, limited studies comparing these noninvasive tests with sphincter of Oddi manometry or outcome after sphincter ablation show only modest correlation. Because of intestinal gas, the pancreatic duct many not be visualized on standard transcutaneous ultrasound. Despite the superiority of endoscopic ultrasound in visualizing the pancreas, Catalano *et al.* report the sensitivity of secretin-stimulated endoscopic ultrasound in detecting SOD to be only 57%.

### Quantitative Hepatobiliary Scintigraphy

Hepatobiliary scintigraphy assesses bile flow through the biliary tract. Impairment to bile flow from sphincter disease, tumors, or stones (as well as parenchymal liver disease) results in impaired radionuclide flow. The precise criteria to define a positive (abnormal) study remain controversial, but duodenal arrival time greater than 20 minutes and hilum to duodenum time greater than 10 minutes are most widely used. Most studies are flawed by lack of correlation with SOM or outcome after sphincter ablation. However, four studies have reported the performance characteristics of hepatobiliary scintigraphy in 105 patients using the results of SOM as the reference standard. The overall

sensitivity was 78% (range, 44–100%), specificity was 90% (range 80–100%), positive predictive value was 92% (range, 82–100%), and negative predictive value was 81% (range, 62–100%). However, these promising results have not been reproduced by other investigators. Overall, it appears that patients with dilated bile ducts and high-grade obstruction are likely to have a positive scintigraphic study. Esber and colleagues found that patients with lower grade obstruction (Hogan–Geenen classification types II and III) generally have normal scintigraphy, even if done after cholecystokinin provocation. Moreover, Pineau *et al.* reported that 8 of 20 asymptomatic control subjects had an abnormal cholecystokinin-stimulated study. The value of hepatobiliary scintigraphy is also limited by the fact that it does not evaluate the pancreatic sphincter.

In the absence of more definitive data, the current conclusion is that noninvasive testing for sphincter of Oddi dysfunction has a relatively low or undefined sensitivity and specificity and is, therefore, not recommended for general clinical use, except in situations when more definitive testing (manometry) is unsuccessful or unavailable.

## DIAGNOSTIC METHODS (INVASIVE)

Because of their associated risks, invasive testing with ERCP and manometry should be reserved for patients with clinically significant or disabling symptoms. In general, invasive assessment of patients for SOD is not recommended unless definitive therapy (sphincter ablation) is planned if abnormal sphincter function is found.

### Cholangiography

Cholangiography is essential to rule out stones, tumors, or other obstructing processes of the biliary tree that may cause symptoms identical to those of SOD. Once such lesions are ruled out by a good quality cholangiographic study, ducts that are dilated and/or drain slowly suggest obstruction at the level of the sphincter. Although some controversy exists, extrahepatic ducts that are greater than 12 mm in diameter (postcholecystectomy), when corrected for magnification, are considered dilated. Although definitive normal supine drainage times have not been well defined, a postcholecystectomy biliary tree that fails to empty all contrast media by 45 minutes is generally considered abnormal.

Endoscopic evaluation of the papilla and periampullary area can yield important information that can influence the diagnosis and treatment of patients with suspected SOD. Occasionally, ampullary cancer may simulate SOD. The endoscopist should do tissue sampling of the papilla (preferably after sphincterotomy) in suspicious cases. Radiographic features of the pancreatic duct are also important to assess in the patient with suspected SOD. Dilation of the pancreatic duct (>6 mm in the pancreatic head and >5 mm in the body) and delayed contrast drainage time (≥9 minutes in the prone position) may give indirect evidence for the presence of SOD.

### Sphincter of Oddi Manometry

The most definitive development in the understanding of the pressure dynamics of the SO came with the advent of sphincter of Oddi manometry. SOM is the only available method to measure SO motor activity directly. Although SOM can be performed intraoperatively and percutaneously, it is most commonly done in the ERCP setting. SOM is considered by most authorities to be the gold standard for evaluating patients for sphincter dysfunction. The use of manometry to detect motility disorders of the sphincter of Oddi is similar to its use in other parts of the gastrointestinal tract. Unlike other areas of the gut, SOM is more technically demanding, invasive, and hazardous. Questions remain as to whether these short-term observations (2- to 10-minute recordings per pull-through) reflect the "24-hour pathophysiology" of the sphincter.

SOM is recommended in patients with idiopathic pancreatitis or unexplained disabling pancreaticobiliary pain with or without hepatic and pancreatic enzyme abnormalities, and to assess for sphincterotomy stenosis or residual sphincter hypertension in symptomatic patients after sphincterotomy is performed for SOD. An ERCP is usually performed (if an adequate study is not available) immediately before the SOM to exclude other potential structural causes for the patient's symptoms. Indications for the use of SOM have also been developed according to the Hogan–Geenen SOD classification System (Table 1). In patients with type I, there is a general consensus that a structural disorder of the sphincter (i.e., sphincter stenosis) exists. Although SOM may be useful in documenting SOD, it is not an essential diagnostic study prior to endoscopic or surgical sphincter ablation. Such patients uniformly benefit from sphincter ablation regardless of the SOM results (see later). Patients with type II demonstrate SO motor dysfunction in 55–65% of cases. In this group of patients, SOM is highly recommended because the results of the study predict outcome from sphincter ablation. Patients with type III have pancreaticobiliary pain without other objective evidence of sphincter outflow obstruction. SOM is mandatory to confirm the presence of SOD. Although

data are limited, it appears that the results of SOM may predict outcome from sphincter ablation in these patients.

SOM is performed by advancing a specialized triple-lumen #5 French water-perfused catheter selectively into the bile duct and/or pancreatic duct. The catheter is pulled across the sphincter zone while pressures are recorded with the aid of a pressure transducer. A variety of modifications of the standard #5 French manometry catheter are commercially available. (The technique of SOM and the interpretation of the tracings are beyond the scope of this discussion.)

It is important to emphasize that complete sphincter assessment requires manometric evaluation of both the biliary and pancreatic sphincters. Current data indicate that an abnormal basal sphincter pressure may be confined to one side of the sphincter in 35–65% of patients. Thus, one sphincter may be dysfunctional whereas the other is normal. Failure to appreciate the anatomically separate pancreatic and biliary sphincters and the potential for discordant manometric results may result in misdiagnosis and improper therapy.

Pancreatitis is the most common major complication after SOM. Using standard perfused catheters, pancreatitis rates as high as 31% have been reported. Such high complication rates have initially limited more widespread use of SOM. These data also emphasize that manometric evaluation of the pancreatic duct is associated with a high complication rate. A variety of methods to decrease the incidence of postmanometry pancreatitis have been developed. In a prospective randomized study, Sherman and colleagues found that the aspirating catheter (this catheter allows for aspiration of the perfused fluid from end and side holes while accurately recording pressure from the two remaining side ports) reduces the frequency of pancreatic duct manometry-induced pancreatitis from 31 to 4%. The reduction in pancreatitis with use of this catheter in the pancreatic duct and the very low incidence of pancreatitis after bile duct manometry lend support to the notion that increased pancreatic duct hydrostatic pressure is a major cause of this complication. Thus, routine aspiration of pancreatic juice should accompany study of the pancreatic duct sphincter by SOM.

### Stent Trial as Diagnostic Test

Placement of a pancreatic or biliary stent on a trial basis in hope of achieving pain relief and predicting the response to more definitive therapy, i.e., sphincter ablation, has received only limited application. Pancreatic stent trials, especially in patients with normal pancreatic ducts, are strongly discouraged because serious ductal and parenchymal injury may occur if stents are left in place for more than a few days. Goff reported a biliary stent trial in 21 type II and type III patients with SOD with normal biliary manometry. Seven French stents were left in place for at least 2 months if symptoms resolved and were removed sooner if they were judged ineffective. Relief of pain with the stent was predictive of long-term pain relief after biliary sphincterotomy. Unfortunately, 38% of the patients developed pancreatitis (14% were graded severe) following stent placement. Because of this high rate of complications, biliary stent trials are strongly discouraged. Rolny and colleagues also reported a series of bile duct stent placements as predictor of outcome following endoscopic sphincterotomy in 23 postcholecystectomy patients (7 type II and 16 type III). Similar to the study by Goff, resolution of pain during at least 12 weeks of stenting predicted a favorable outcome from sphincterotomy irrespective of sphincter of Oddi pressure. In this series there were no complications related to stent placement.

## THERAPY FOR SOD

The therapeutic approach in patients with SOD is aimed at reducing the resistance caused by the sphincter of Oddi to the flow of bile and/or pancreatic juice. Historically, most emphasis has been placed on definitive intervention, i.e., surgical sphincteroplasty or endoscopic sphincterotomy. This appears appropriate for patients with high-grade obstruction (type I as per Hogan–Geenen criteria). In patients with lesser degrees of obstruction, the clinician must carefully weigh the risks and benefits before recommending invasive therapy.

### Medical Therapy

Medical therapy for documented or suspected SOD has received only limited study. Because the SO is a smooth muscle structure, it is reasonable to assume that drugs that relax smooth muscle might be an effective treatment for SOD. Sublingual nifedipine and nitrates have been shown to reduce the basal sphincter pressures in asymptomatic volunteers and symptomatic patients with SOD. Although medical therapy may be an attractive initial approach in patients with SOD, several drawbacks exist. First, medication side effects may be seen in up to one-third of patients. Second, smooth muscle relaxants are unlikely to be of any benefit in patients with the structural form of SOD (i.e., SO ste-

nosis) and the response is incomplete in patients with a primary motor abnormality of the SO (i.e., SO dyskinesia). Finally, long-term outcome from medical therapy has not been reported. Nevertheless, because of the "relative safety" of medical therapy and the benign (though painful) character of SOD, this approach should be considered in all type III and less severely symptomatic type II SOD patients before considering more aggressive sphincter ablation therapy.

## Surgical Therapy

The surgical approach, most commonly, is a transduodenal biliary sphincteroplasty with a transampullary septoplasty (pancreatic septoplasty). Some 60–70% of patients were reported to have benefited from this therapy during a 1- to 10-year followup. Patients with an elevated basal sphincter pressure determined by intraoperative SOM were more likely to improve from surgical sphincter ablation than were those with a normal basal pressure. Some reports have suggested that patients with biliary-type pain have a better outcome than do patients with idiopathic pancreatitis, whereas others have suggested no difference. However, most studies found that symptom improvement following surgical sphincter ablation alone was relatively uncommon in patients with established chronic pancreatitis. The surgical approach for SOD has largely been replaced by endoscopic therapy. Patient tolerance, cost of care, morbidity, mortality, and cosmetic results are some of the factors that favor an initial endoscopic approach. At present, surgical therapy is reserved for patients with restenosis following endoscopic sphincterotomy and when endoscopic evaluation and/or therapy are not available or technically feasible.

## Endoscopic Therapy

Endoscopic sphincterotomy is the current standard therapy for patients with SOD. Most data on endoscopic sphincterotomy relate to biliary sphincter ablation alone. Clinical improvement following therapy has been reported to occur in 55–95% of patients (Table I). These variable outcomes are reflective of the different criteria used to document SOD, the degree of obstruction (type I biliary patients appear to have a better outcome than do types II and III), the methods of data collection (retrospective vs. prospective), and the techniques used to determine benefit. Rolny and colleagues studied 17 type I postcholecystectomy biliary patients by SOM. In this series, 65% had an abnormal SOM (although not specifically stated, it appears that the biliary sphincter was studied alone). Nevertheless, during a mean followup interval of 2.3 years, all patients benefited from biliary sphincterotomy. The results of this study suggest that because type I biliary patients invariably benefit from biliary sphincterotomy, SOM in this patient group is not only unnecessary, but it may also be misleading. The results of this study, however, have never been validated at another center.

Although most of the studies reporting efficacy of endoscopic therapy in SOD have been retrospective, three notable randomized trials have now been reported. In a landmark study by Geenen and associates, 47 postcholecystectomy type II biliary patients were randomized to biliary sphincterotomy or sham sphincterotomy. SOM was performed in all patients but was not used as a criterion for randomization. During a 4-year followup, 95% of patients with an elevated basal sphincter benefited from sphincterotomy. In contrast, only 30–40% of patients with an elevated sphincter pressure treated by sham sphincterotomy or with a normal sphincter pressure treated by endoscopic sphincterotomy or sham sphincterotomy benefited from this therapy. The two important findings of this study were that SOM predicted the outcome from endoscopic sphincterotomy and that endoscopic sphincterotomy offered long-term benefit in type II biliary patients with SOD.

Sherman and associates reported their preliminary results of a randomized study comparing endoscopic sphincterotomy, surgical biliary sphincteroplasty with pancreatic septoplasty (with or without cholecystectomy), to sham sphincterotomy for type II and type III biliary patients with manometrically documented SOD. During a 3.0-year followup period, 69% of patients undergoing endoscopic or surgical sphincter ablation improved, compared to 24% in the sham sphincterotomy group ($p = 0.009$). There was a trend for type II patients to benefit more frequently from sphincter ablation, compared to type III patients [13/16 (81%) vs. 11/19 (58%); $p = 0.14$]. Evidence is now accumulating that the addition of a pancreatic sphincterotomy to an endoscopic biliary sphincterotomy in such patients may improve the outcome (see later).

In a third study, postcholecystectomy patients with biliary-type pain (mostly type II) were prospectively randomized to endoscopic sphincterotomy or sham following stratification according to SOM. Of patients with elevated basal pressure, 85% (11 of 13) improved at 2 years after endoscopic sphincterotomy, whereas 38% (5 of 13) of patients improved after a sham procedure ($p = 0.041$).

There are numerous nonrandomized trials reporting benefit rates of 56–78% in type II patients with manometrically documented SOD treated with biliary sphincterotomy. The benefit rate in type III patients was more variable but the number of patients treated was relatively small. Untreated pancreatic sphincter hypertension appears to be one of the reasons that patients with SOD fail to benefit from biliary sphincterotomy alone. Because there are separate biliary and pancreatic sphincters, ablation of the biliary sphincter alone usually leaves the pancreatic sphincter pressure unaltered. Surgeons have appreciated this for years, and this accounts for the common surgical approach of a biliary and pancreatic sphincteroplasty. Eversman and colleagues found that 90% of SOD patients with persistent pain or pancreatitis after biliary sphincterotomy had residual abnormally elevated pancreatic sphincter pressure. This same group reported that 80% of SOD patients with isolated elevated biliary sphincter pressure (normal pancreatic sphincter pressure) were clinically improved at 5-year followup after biliary sphincterotomy alone, whereas only 48% of patients with elevated basal pancreatic sphincter pressure (with normal or abnormal basal biliary sphincter pressure) benefited from this therapy. Evidence is now accumulating that the addition of an endoscopic pancreatic sphincterotomy to a biliary sphincterotomy in patients with SOD may improve outcome. This will be discussed further in the following sections.

These results clearly indicate that the response rate and enthusiasm for sphincter ablation must be correlated with patient presentation and balanced against the high complication rates reported for endoscopic therapy of SOD. Most studies indicate that patients undergoing endoscopic sphincterotomy for SOD have complication rates two to five times higher compared to patients undergoing endoscopic sphincterotomy for ductal stones. Pancreatitis is the most common complication, occurring in up to 20% of patients. Endoscopic techniques are being developed (e.g., pancreatic duct stenting prior to combined pancreaticobiliary sphincterotomy and pancreatic stenting after biliary sphincterotomy) to limit such complications.

### Balloon Dilation and Stenting

In an attempt to be less invasive and possibly preserve sphincter function, adaptation of this technique to treat SOD has been described. Unfortunately, because of the unacceptably high complication rates, primarily pancreatitis, this technology has little role in the management of SOD. Similarly, although biliary stenting might offer short-term symptom benefit in patients with SOD and predict outcome from sphincter ablation, it, too, has unacceptably high complication rates and cannot be advocated in this setting based on the available data.

### Botulinum Toxin Injection

Botulinum toxin (Botox), a potent inhibitor of acetylcholine release from nerve endings, has been successfully applied to smooth muscle disorders of the gastrointestinal tract such as achalasia. In a preliminary clinical trial, Botox injection into the SO resulted in a 50% reduction in the basal sphincter pressure and improved bile flow. This reduction in pressure may be accompanied by symptom improvement in some patients. It follows that Botox may serve as a therapeutic trial for SOD, with responders undergoing permanent sphincter ablation. One such study was recently reported. Twenty-two postcholecystectomy type III patients with manometric evidence of SOD underwent Botox injection into the intraduodenal sphincter segment. Overall, 11 of the 12 patients who responded to Botox, versus 2 of 10 patients who did not gain pain relief, later benefited from endoscopic sphincterotomy ($p < 0.01$). Such an approach, however, does require at least two procedures, each with their associated complications.

## SOD IN RECURRENT PANCREATITIS

SOD has been manometrically documented in 15–72% of patients with recurrent pancreatitis, previously labeled as idiopathic. Biliary sphincterotomy alone has been reported to prevent further pancreatitis episodes in more than 50% of such patients. The value of ERCP, SOM, and sphincter ablation therapy was studied in 51 patients with idiopathic pancreatitis; 24 (47.1%) had an elevated basal sphincter pressure and 30 were treated by either biliary sphincterotomy ($n = 20$) or surgical sphincteroplasty with pancreatic septoplasty ($n = 10$). Of these patients, 15 of 18 (83%) with an elevated basal sphincter pressure had long-term benefit (mean followup, 38 months) from sphincter ablation therapy (including 10 of 11 treated by biliary sphincterotomy), in contrast to only 4 of 12 (33.3%, $p < 0.05$) with a normal basal sphincter pressure (including 4 of 9 treated by biliary sphincterotomy). Guelrud *et al.*, however, found that severance of the pancreatic sphincter was necessary to resolve the pancreatitis (Table II). In this series, 69 patients with idiopathic pancreatitis due to SOD underwent treatment by standard biliary

**TABLE II Pancreatic Sphincter Dysfunction and Recurrent Pancreatitis: Response to Sphincter Therapy**

| Treatment | Number of patients improved/total number of patients |
|---|---|
| Biliary sphincterotomy alone | 5/18 (28%) |
| Biliary sphincterotomy followed by pancreatic sphincter balloon dilation | 13/24 (54%) |
| Biliary sphincterotomy plus pancreatic sphincterotomy at later session | 10/13 (77%)[a] |
| Biliary sphincterotomy and pancreatic sphincterotomy at same session | 12/14 (86%)[a] |

[a] $p < 0.005$ vs. biliary sphincterotomy alone.

sphincterotomy ($n = 18$), biliary sphincterotomy with pancreatic sphincter balloon dilation ($n = 24$), biliary sphincterotomy followed by pancreatic sphincterotomy in separate sessions ($n = 13$), or combined pancreatic and biliary sphincterotomy in the same session ($n = 14$). Eighty-one percent of patients undergoing pancreatic and biliary sphincterotomy had resolution of their pancreatitis compared to 28% of patients undergoing biliary sphincterotomy alone ($p < 0.005$). These data are consistent with the theory that many such patients who benefit from biliary sphincterotomy alone have subtle gallstone pancreatitis. The results of Guelrud *et al.* also support the anatomic findings of separate biliary and pancreatic sphincters, and the manometry findings of residual pancreatic sphincter hypertension in more than 50% of persistently symptomatic patients who undergo biliary sphincterotomy alone. Toouli *et al.* also demonstrated the importance of pancreatic and biliary sphincter ablation in patients with idiopathic pancreatitis. In this series, 23 of 26 patients (88%) undergoing surgical ablation of both the biliary and pancreatic sphincter were either asymptomatic or had minimal symptoms at a median followup of 24 months (9–105 months). A different group retrospectively evaluated the long-term results of endoscopic pancreatic sphincterotomy in 55 patients with presumed (recurrent pancreatitis with pancreatic duct dilation and contrast medium drainage time from the pancreatic duct greater than 10 minutes) or manometrically documented pancreatic sphincter dysfunction. During a median followup of 16 months (range, 3–52 months), 34 patients (62%) reported significant pain improvement. Patients with normal pancreatograms were more likely to respond to therapy than were those with pancreatographic evidence of chronic pancreatitis (73 vs. 58%).

Currently, the best method to treat residual pancreatic sphincter stenosis after biliary sphincterotomy awaits further study. Patients with idiopathic pancreatitis who fail to respond to biliary sphincterotomy alone should have their pancreatic sphincter reevaluated and be considered for sphincter ablation if residual high pressure is found.

## SOD IN PATIENTS WITH INTACT GALLBLADDER

SOD may exist in the presence of an intact biliary tract with the gallbladder *in situ*. Because the symptoms of SO or gallbladder dysfunction cannot be readily separated, the diagnosis of SOD is commonly made after cholecystectomy or less frequently after proper investigations have excluded gallbladder abnormalities. The frequency of manometrically documented SOD in patients prior to cholecystectomy has received limited study. Guelrud and colleagues studied 121 patients with symptomatic gallstones and a normal common bile duct diameter (by transcutaneous ultrasound) by SOM prior to cholecystectomy. An elevated basal sphincter pressure was found in 14 patients (11.6%). SOD was diagnosed in 4.1% of patients with a normal serum alkaline phosphatase (4 of 96) and in 40% with an elevated serum alkaline phosphatase (10 of 25). Ruffolo *et al.* evaluated 81 patients with symptoms suggestive of biliary disease but normal ERCP and no gallbladder stones on transcutaneous ultrasound by scintigraphic gallbladder ejection fraction and endoscopic SOM. Fifty-three percent of patients had SOD and 49% had an abnormal gallbladder ejection fraction. SOD occurred with a similar frequency in patients with an abnormal gallbladder ejection fraction (50%) and a normal ejection fraction (57%).

The approach to patients with suspected SOD and intact gallbladder is frequently a challenging problem. In patients that have a clearly abnormal gallbladder ejection fraction (GBEF) of less than 35%, it seems prudent to proceed with laparoscopic cho[illegible]y. In patients with a low GBEF, this approach ma[illegible]ovide relief of symptoms for 70–80% of patients. Although there is some evidence that cholecystectomy may exacerbate SOD by loss of the gallbladder reservoir function and decreased compliance, the risks of laparoscopic cholecystectomy are less than those of ERCP with SOM. Patients with a borderline or normal GBEF present a diagnostic and therapeutic dilemma as well. A recent study has suggested that symptom reproduction

after CCK infusion may be as important as GBEF in the evaluation of ultrasound-negative biliary colic. These results would tend to favor a trial of cholecystectomy before proceeding with SOM in patients with intact gallbladder and suspected SOM. The GBEF may be misleading in patients who have had previous biliary sphincterotomy, with a lack of gallbladder filling seen in 75% postsphincterotomy.

## FAILURE TO ACHIEVE SYMPTOMATIC IMPROVEMENT AFTER BILIARY SPHINCTEROTOMY

There are several potential explanations as to why patients may fail to achieve symptom relief after biliary sphincterotomy is performed for well-documented sphincter of Oddi dysfunction. First, the biliary sphincterotomy may have been inadequate or restenosis may have occurred. Although the biliary sphincter is commonly not totally ablated, one study indicates that clinically significant biliary restenosis occurs relatively infrequently. If no "cutting space" remains in such a patient, balloon dilation to 8–10 mm may suffice, but long-term outcome from such therapy is unknown.

Second, the importance of pancreatic sphincter ablation is being increasingly recognized. One report has shown that 25 of 26 patients (mostly type II), who failed to respond to biliary sphincterotomy, had elevated pancreatic sphincter pressure. Endoscopic pancreatic sphincterotomy was performed with overall symptomatic improvement in two-thirds of patients. Another group performed pancreatic sphincterotomy on 43 type I and type II SOD patients who failed to benefit from biliary sphincterotomy alone. During the followup period, 72% were symptom free and 19% were partially or transiently improved. A study by a different group also presented data demonstrating that response to sphincterotomy depends on treating the diseased sphincter segment. Specifically, the outcome from biliary sphincterotomy alone depended on whether the biliary, pancreatic, or both sphincters were abnormal. Patients with pancreatic sphincter hypertension who fail to improve from biliary sphincterotomy alone can be "rescued" by undergoing pancreatic sphincterotomy. In this study, 80% of patients with isolated biliary sphincter hypertension benefited from biliary sphincterotomy during a 17-month followup period. In contrast, 15% of patients with isolated pancreatic sphincter hypertension and 50% with combined sphincter disease improved. However, when patients with persistent symptoms and elevated basal pancreatic sphincter pressure were then treated with a pancreatic sphincterotomy, the improvement rate was 77% for the group with isolated pancreatic sphincter hypertension and 80% for the group with combined sphincter disease. Overall, 79% of patients improved after a biliary sphincterotomy and selective pancreatic sphincterotomy, compared with a 45% benefit rate if only biliary sphincterotomy was done.

A third explanation as to why patients may fail to respond to sphincterotomy is because they have chronic pancreatitis. These patients may or may not have abnormal pancreatograms. Endoscopic ultrasound may show parenchymal and ductular changes of the pancreas in some of these patients, suggesting chronic pancreatitis. Finally, some patients may be having pain from altered gut motility of the stomach, small bowel, or colon (irritable bowel or pseudo-obstruction variants). There is increasing evidence that upper gastrointestinal motility disorders may masquerade as pancreatobiliary-type pain (i.e., discrete right upper quadrant pain). Multiple preliminary studies show disordered duodenal motility in such patients. This area needs much more study to determine the frequency, significance, and/or coexistence of these motor disorders along with SOD. A recent study suggested that type III patients have duodenal specific visceral hyperalgesia with pain reproduction by duodenal distension. These patients were also shown to have high levels of somatization, depression, obsessive–compulsive behavior, and anxiety compared to control subjects.

## SUMMARY

In summary, our knowledge of sphincter of Oddi dysfunction and manometric techniques to assist in this diagnosis are evolving. Successful endoscopic SOM requires good general ERCP skills and careful attention to the main details involved. If SOD is suspected in a type III or mild to moderate pain level type II patient, medical therapy should generally be tried. If medical therapy fails or is bypassed, ERCP and manometric evaluation are recommended. The role of less invasive studies remains uncertain due to undefined sensitivity and specificity. Sphincter ablation is generally warranted in symptomatic type I patients and type II and type III patients with abnormal manometry. The symptom relief rate varies from 55 to 95%, depending on the patient presentation and selection. Initial nonresponders require thorough pancreatic sphincter and pancreatic parenchymal evaluation. SOD patients have relatively high complication rates after invasive studies or therapy. Thorough review of the risk:benefit ratio with individual patients is mandatory.

## Acknowledgment

The authors are grateful to Tina Jackson for the technical preparation of this document.

## See Also the Following Articles

**Biliary Tract, Anatomy • Manometry • Pancreatitis, Chronic • Sphincters • Sphincterotomy**

## Further Reading

Chen, J. W. C., Saccone, G. T. P., and Toouli, J. (1998). Sphincter of Oddi manometry in the diagnosis and therapy of pancreatic disease. *Gastrointest. Endosc. Clin. North Am.* **8**, 79–85.

Eversman, D., Fogel, E., Rusche, M., Sherman, S., and Lehman, G. A. (1999). Frequency of abnormal pancreatic and biliary sphincter manometry compared with clinical suspicion of sphincter of Oddi dysfunction. *Gastrointest. Endosc.* **50**, 637–641.

Fogel, E. L., and Sherman, S. (2000). Performance of sphincter of Oddi manometry. *Clin. Perspect. Gastroenterol.* **4**, 165–173.

Freeman, M. L., Nelson, D. B., Sherman, S., *et al.* Complications of endoscopic biliary sphincterotomy. (1996). *N. Engl. J. Med.* **335**, 909–918.

Geenen, J. E., Hogan, W. J., Dodds, W. J., Toouli, J., and Venu, R. P. (1989). The efficacy of endoscopic sphincterotomy after cholecystectomy in patients with suspected sphincter of Oddi dysfunction. *N. Engl. J. Med.* **320**, 82–87.

Hogan, W., Sherman, S., Pasricha, P., and Carr-Locke, D. L. (1997). Position paper on sphincter of Oddi manometry. *Gastrointest. Endosc.* **45**, 342–348.

Kalloo, A. N., and Pasricha, P. J. (1996). Therapy of sphincter of Oddi dysfunction. *Gastrointest. Endosc. Clin. North Am.* **6**, 117–125.

Kuo, W. H., Pasricha, P. J., and Kalloo, A. N. (1998). The role of sphincter of Oddi manometry in the diagnosis and therapy of pancreatic disease. *Gastrointest. Endosc. Clin. North Am.* **8**, 79–85.

Sherman, S. (2002). What is the role of ERCP in the setting of abdominal pain of pancreatic or biliary origin (suspected sphincter of Oddi dysfunction)? *Gastrointest. Endosc.* **56**, S258–S266.

Sherman, S., Troiano, F. P., Hawes, R. H., *et al.* (1990). Sphincter of Oddi manometry—Decreased risk of clinical pancreatitis with the use of modified aspirating catheter. *Gastrointest. Endosc.* **36**, 462–466.

Sostre, S., Kalloo, A. N., Spiegler, E. J., Camargo, E. E., and Wagner, H. N. (1992). A noninvasive test of sphincter of Oddi dysfunction in postcholecystectomy patients: The scintigraphic score. *J. Nucl. Med.* **33**, 1216–1222.

Wehrmann, T., Seifert, H., Seipp, M., Lembcke, B., and Caspary, W. F. (1998). Endoscopic injection of botulinum toxin for biliary sphincter of Oddi dysfunction. *Endoscopy* **30**, 702–707.

# Sphincterotomy

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retroperitoneum The space behind the peritoneal cavity and anterior to the muscles and bones of the back, wherein reside the blood vessels, nerves, and lymph nodes associated with the abdominal viscera.
splanchnic nerve Nerves transmitting pain of visceral origin.

**Sphincterotomy is the division of the specialized muscle fibers defining an aperture. In the gastrointestinal tract, the two sphincters typically divided are the sphincter of Oddi and the internal anal sphincter. The aperture (ampulla) defined by the sphincter of Oddi is that at which the common bile duct and pancreatic duct enter the duodenum. The internal anal sphincter preserves fecal continence and is located between the anal canal and the external environment.**

## DIVISION OF THE SPHINCTER OF ODDI

Patients in whom division of the sphincter of Oddi is performed typically have symptoms referable to obstruction of the biliary tree (jaundice with or without pain, dark urine, light stools) and laboratory studies suggesting obstruction (elevation of the direct bilirubin, alkaline phosphatase, and/or amylase levels). Inflammation of the pancreas or stones of biliary or pancreatic origin causing obstruction typically have associated pain and fever. Obstructions secondary to benign or malignant tumor occluding the sphincter of Oddi classically present with painless jaundice and weight loss from malabsorptive malnutrition. Pain associated with malignant obstruction typically indicates surgically unresectable, advanced disease and splanchnic nerve involvement from tumor ingrowth into the splanchnic nerves of the retroperitoneum.

Division of the sphincter of Oddi (sphincterotomy) is most typically performed with cold knife or electrocautery endoscopically introduced into the sphincteral lumen and withdrawn through one side of the lumen. If the sphincter is tight and precludes cannulation by this method, a "pre-cut" technique may be used, where endoscopic incision in the bile duct is made through the common wall between the duodenum and the bile duct. This incision is then carried to the ampulla. Sphincterotomy both facilitates bile flow and allows access to the common duct so that impacted stones might be removed or radiographic visualization of the biliary and pancreatic ducts might be accomplished. The radiologic visualization of these ducts through endoscopically guided retrograde injection of contract is known as endoscopic retrograde cholangiopancreatography. Visualization of the bile duct may be diagnostic and determine whether surgery is necessary for stone or stricture; if obstruction of the bile duct has occurred from a benign process, the sphincterotomy itself may also be therapeutic and obviate the need for open surgical intervention. In such instances, the sphincterotomy or associated stone extraction relieves the patient's obstructive symptoms.

Resting sphincter tone is decreased following sphincterotomy. Although this often leads to some low level of continuous flow of bile into the duodenum, additional relaxation of the sphincter still accompanies the ingestion of a meal.

## DIVISION OF THE LATERAL INTERNAL ANAL SPHINCTER

The continence mechanism for fecal material involves an anatomic and physiologic fusion of the anorectum's longitudinal and circular muscle fibers with the levator ani muscles and those of the puborectalis sling. Anal fissure is a painful tear in the anal sphincter. Typically seen in patients with constipation, the established fissure is recognizable by the typical linear tear in the posterior midline and associated skin tag (sentinel pile) just distal to the tear.

Division of the internal anal sphincter, as described by Parks, breaks the cycle of pain, spasm, and recurrent tearing, reducing resting anal pressures by 25–50% for at least 4–6 years postoperatively.

The procedure may be performed under a general, regional, or local anesthetic. Rather than dividing the internal sphincter directly over the fissure, a lateral site for the incision is chosen. The sphincter may be divided by direct visualization through an incision made over it or as a blind procedure wherein a knife is insinuated

 

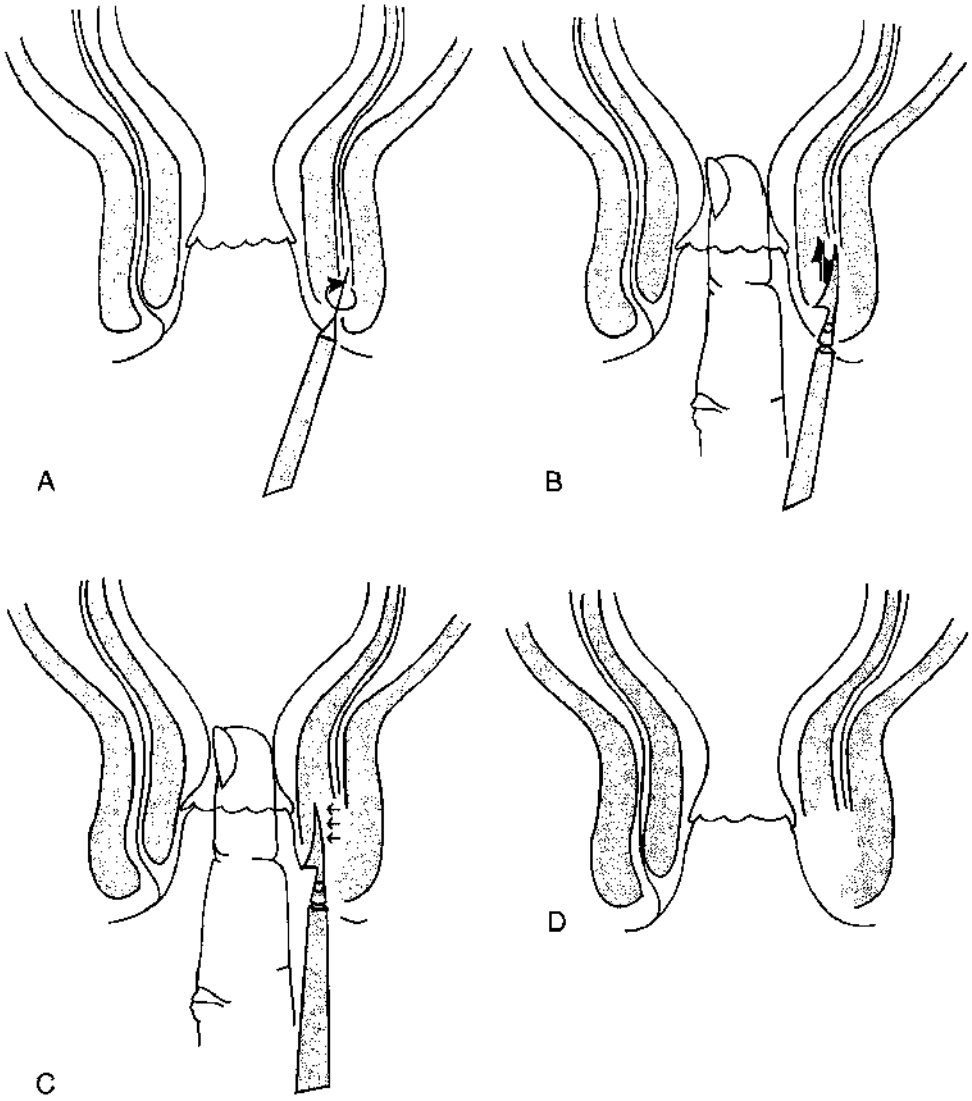


FIGURE 1 The scalpel is placed through a lateral stab wound made between the external and internal anal sphincters (A). It is rotated (B) and advanced in a sawing motion to approach the mucosa and the examining finger (C). The completed distal lateral sphincterotomy is shown in D.

between the external and internal sphincters (the intersphincteric groove) and the internal sphincter is divided with a finger in the rectum to avoid entry into the anal canal and creation of a fistula-in-ano (Fig. 1). The resultant decrease in tone facilitates spontaneous healing of both the surgical wound and the original fissure. The procedure is rarely associated with incontinence of solid stool or gas; fewer than 1% of patients experience incontinence of mucous or of liquid stool.

## See Also the Following Articles

**Anal Sphincter • Bile Duct Injuries and Fistulas • Sphincter of Oddi Dysfunction • Stents**

## Further Reading

American Society for Gastrointestinal Endoscopy (1999). The role of ERCP in diseases of the biliary tract and pancreas: Guidelines for clinical application. *Gastrointest. Endosc.* **50**, 915–920.

Bennett, R. C., and Goligher, J. C. (1962). Results of internal sphincterotomy for anal fissure. *Br. Med. J.*, 1500–1503.

Hoffman, D. C., and Goligher, J. C. (1970). Lateral subcutaneous internal sphincterotomy in the treatment of anal fissure. *Br. Med. J.* 3. 673–675.

Parkes, A. G. (1967). The management of fissure-in-ano. *Hosp. Med.* 1, 737.

# Sphincters

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**reflux** Backward flow or movement, as in reflux of contents from the stomach into the esophagus.
**sphincter** Ring of circular muscle surrounding and closing an orifice.

**Sphincters are present in a variety of locations along the digestive tract. Some of the sphincters are composed of skeletal muscle, others are composed of smooth muscle. Skeletal muscle sphincters are controlled by the central nervous system. Smooth muscle sphincters are controlled by the enteric nervous system. There are two skeletal muscle sphincters, the upper esophageal sphincter and the external anal sphincter. Smooth muscle sphincters are found at the gastroesophageal junction, gastroduodenal junction, ileocolonic junction, and termination of the large intestine in the anus.**

## SMOOTH MUSCLE SPHINCTERS

Smooth muscle sphincters consist of rings of muscle that remain in a continuous state of contraction. Specialized "latch" mechanisms in the contractile filaments enable sphincters to maintain contractile tone for extended periods with minimal expenditure of energy. The effect of the tonic contractile state is to occlude the lumen in a region that separates two specialized compartments. With the exception of the internal anal sphincter, sphincters function to prevent the backward movement of intraluminal contents. The internal anal sphincter prevents uncontrolled movement of intraluminal contents through the anus.

The lower esophageal sphincter prevents reflux of gastric acid into the esophagus. Incompetence results in chronic exposure of the esophageal mucosa to acid, which can lead to heartburn and dysplastic changes that may become cancerous. The gastroduodenal sphincter, which is sometimes called the pyloric sphincter, prevents excessive reflux of duodenal contents into the stomach. Incompetence of this sphincter can result in the reflux of bile acids and proteolytic enzymes from the duodenum. Bile acids and proteolytic enzymes are damaging to the protective barrier in the gastric mucosa: prolonged exposure can lead to gastritis and ulceration.

The ileocolonic sphincter prevents reflux of colonic contents into the ileum. Incompetence can allow entry of bacteria into the ileum from the colon and may result in bacterial overgrowth. Bacterial counts are normally low in the small intestine.

## ENTERIC NERVOUS CONTROL

The ongoing contractile tone in the smooth muscle sphincters is generated by myogenic mechanisms. The contractile state is an inherent property of the muscle and is independent of the nervous system. Transient relaxation of the sphincter to permit the forward passage of material is accomplished by activation of enteric inhibitory motor neurons that innervate the sphincteric musculature.

The inhibitory innervation of the smooth muscle sphincters is transiently activated for timed opening and passage of luminal contents. Smooth muscle sphincters remain tonically contracted, occluding the lumen and thereby preventing the passage of contents between adjacent compartments (e.g., between stomach and esophagus). The inhibitory neurons that innervate the sphincter are normally inactive and are switched on with timing appropriate for coordination of the opening of the sphincter with physiological events in adjacent regions. When this occurs, the inhibitory neurotransmitter relaxes the ongoing muscle contraction in the sphincteric muscle and prevents excitation-contraction in the adjacent muscle from spreading into and closing the sphincter. Damage to or loss of the inhibitory innervation of smooth muscle sphincters results in failure of the sphincter to relax. This results in the sphincter becoming a barrier to the onward passage of the luminal contents from compartment to compartment.

### See Also the Following Articles

**Achalasia • Barrett's Esophagus • Belching • Defecation • Disinhibitory Motor Disorder • Dysphagia • Enteric Nervous System • Fecal Incontinence • Flatulence • Gastroesophageal Reflux Disease (GERD) • Pylorus • Rumination Syndrome • Swallowing**

## Further Reading

Papasova, M. (1989). Sphincteric function. *In* "Handbook of Physiology, The Gastrointestinal System I" (J. Wood, ed.), Sect. 6, Vol. 1, Part 2, pp. 987–1023. American Physiological Society, Bethesda.

Wood, J. (2003). Neurogastroenterology and gastrointestinal motility. *In* "Medical Physiology" (R. Rhoades and G. Tanner, eds.), 2nd Ed., Chap. 26, pp. 449–480. Lippincott Williams & Wilkins, Baltimore.

# Splenectomy

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**autoantibody** An antibody directed against oneself.
**cross-sectional imaging** Radiologic studies such as computed tomography or magnetic resonance imaging, which display the relevant anatomy as a series of "slices" from which three-dimensional relationships can be inferred.
**encapsulated organisms** Bacteria with a well-developed cell wall (e.g., pneumococcus).
**hematopoiesis** Creation of the formed elements of the blood (e.g., red corpuscles).
**sequestration** Retention of formed elements of the blood as they pass through the spleen, often leading to their destruction or to enlargement of the spleen.

**The normal spleen is a fist-sized organ located beneath the left hemidiaphragm. It has immunologic, hematopoietic, and filtering functions, which vary with the patient's age; alteration in these functions in disease may cause recognizable syndromes characterized by changes in splenic size, synthesis and sequestration of the formed elements of the blood, and rate of removal of formed elements of the blood from the circulation. Splenectomy may be indicated for irreparable splenic injury, multiple organ injury, hyperfunction, increase in size, splenic neoplasm, splenic abscess, or aneurysm of the splenic artery. Removal of the spleen is accompanied by increased systemic susceptibility to infection, particularly with encapsulated organisms and particularly in young patients.**

## INJURY TO THE SPLEEN

The spleen may be injured with a blunt blow to the abdomen with or without overlying rib fracture. Rarely, it may rupture with infectious diseases such as infectious mononucleosis. In cases of rib fracture, the injury caused by the penetrating fragments may be similar to that occasioned by a traversing missile or by impalement. In penetrating injury, suspicion of splenic injury is further aroused by signs and symptoms of blood loss in the presence of broken ribs or an appropriate trajectory of the penetrating foreign body. In blunt trauma, rib fracture, mechanism of injury, or Kehr's sign (left shoulder pain from ipsilateral diaphragmatic irritation) may also raise suspicion. Significant red blood cells in the peritoneum on lavage or fluid on diagnostic ultrasound with a plausible mechanism of injury may suggest the need for laparotomy, as may more specific evidence of organ injury on cross-sectional imaging. Isolated splenic injuries do not require splenectomy in all cases; some that do not involve the hilum may be managed without laparotomy and some injuries may be successfully repaired at laparotomy. When the spleen is one of multiple intra-abdominal organs injured, particularly when one of the others is the colon, splenectomy is preferable to splenic preservation. Although splenectomy for some elective indications may be performed laparoscopically, almost all splenectomies for trauma are performed by open laparotomy because of the hemodynamic urgency of the situation (hemorrhagic shock) and the concomitant difficulties in inspecting both the spleen and the other organs by a laparoscopic approach in the presence of significant blood loss.

Because of its intimate relationship with the colon as this viscus passes through the left upper quadrant and because of the proximity of the spleen to the left kidney, left adrenal, pancreatic tail, and greater curvature of the

stomach, surgery on these organs may produce splenic injury. Most such injuries can be repaired, but persistent bleeding or deep instrumental injury may require splenectomy for hemorrhage control.

## SPLENECTOMY FOR ANEMIA

Hereditary spherocytosis is an autosomal dominant disease related to bonding deficiencies of the proteins of the red blood cell membrane. Red cells lose their deformability due to this abnormality and become round (spherocytes) or elliptical (elliptocytes) when viewed on smears of the peripheral blood. Shearing of the red blood cell membrane on passage of blood through the spleen results in an anemia with associated jaundice, reticulocytosis, splenomegaly, and occasionally pigmented gallstones as the aberrant cells are removed from the circulation. Diagnosis is made by examination of the peripheral smear in the proper clinical setting. Splenectomy relieves the anemia, but the cellular deformity persists.

Another autosomally inherited disease, thalassemia, also produces cellular membrane rigidity, but in this case by precipitation of excessive α-hemoglobin chains in the presence of decreased production of β-chains. Sequestration of blood in the splenic cords results in intrasplenic hemolysis of red cells, enlargement of the spleen, and tenderness. Removing the spleen surgically addresses the component of the anemia occasioned by the mechanical lysis, but not that occasioned by the production of the abnormal hemoglobin.

In congenital anemias, an attempt is made to defer removal of the organ well into childhood because of concerns related to overwhelming postsplenectomy sepsis. Removal of the organ before the age of 4 years is justified only by severe disease manifestations.

## IMMUNOLOGIC REASONS FOR SPLENECTOMY

The immunologic "tagging" of the formed elements of the blood for premature removal by the spleen is the descriptive explanation offered for the low platelet counts of idiopathic thrombocytopenic purpura (ITP) and the acquired hemolytic anemias. In ITP, determination of the circulating platelet count in patients with petechial hemorrhage in the skin or mucous membranes, bleeding without trauma, or bleeding out of proportion to injury establishes the diagnosis of thrombocytopenia; bone marrow aspirates showing megakaryocytes and the absence of a pharmacologic reason for thrombocytopenia support the diagnosis. Splenectomy is reserved for patients failing courses of steroids or other medical treatment or those requiring chronic steroid administration to maintain an adequate platelet count. Splenectomy is successful in raising the platelet count to asymptomatic levels in 70% of patients; the other 30% presumably retain immunoglobulin G (IgG)-mediated platelet-destructive mechanisms in other organs.

If the IgG autoantibody tags red blood cell membrane proteins, red cells adhere to splenic macrophages, which destroy them. Steroids again are the front-line treatment, with salvage splenectomy in the event of failure of medical management producing favorable responses in the ranges reported for ITP.

A splenectomy is effective for hemolytic anemia only if the antibodies are warm-reacting; hemolysis for cold-reacting antibodies is IgM-mediated and occurs intravascularly rather than within the spleen. As with ITP, the persistence of IgG (warm antibody)-mediated hemolysis after splenectomy indicates a robust macrophage depot elsewhere in the reticuloendothelial system, liver, or bone marrow.

## MECHANICAL HYPERSPLENISM

Hypersplenism is a condition characterized by pancytopenia and splenomegaly in the presence of an active bone marrow. Primary treatment is administration of corticosteroids, with splenectomy reserved for pharmacologic failure.

When the abnormal cells of a myeloproliferative disorder, lipid storage disease, or lymphoproliferative disorder infiltrate the splenic red pulp, blood flow through the organ is diminished, leading to red blood cell glucose deprivation and cell death by hemolysis. To the extent that the marrow is infiltrated as well, failure of red cell production may augment the anemia. Production of other formed elements may also be suppressed by the infiltrate. Splenectomy produces variable results, depending on whether extramedullary hematopoiesis augments formed element counts, and is usually preceded by a course of steroids or chemotherapy. When salutary, it provides symptomatic relief (as the palpable and symptomatic enlargement of such spleens leads to early satiety) and may facilitate the administration of drugs to treat the primary disorder.

The spleen is often enlarged as part of the rise in tributary pressures of the valveless portal system in patients with portal hypertension. When asymptomatic, splenectomy for enlargement alone is not indicated. Splenic vein decompression with portasystemic shunt or transjugular intrahepatic portasystemic shunt, rather than splenectomy, is the treatment is of choice for thrombocytopenic portal hypertensive patients if the splenic vein is patent. In cases where bleeding gastric varices occur because of splenic vein thrombosis,

splenectomy ameliorates the bleeding in controlling back pressure from the thrombosed splenic vein, which is transmitted to the gastric varix. It is by this decompression that the hemorrhage abates.

Splenectomy for mechanical hypersplenism carries an operative mortality rate of 15–30%, as opposed to less than 5% for elective splenectomy for nonmechanical causes.

## MISCELLANEOUS REASONS FOR SPLENECTOMY

The spleen may be an embolic site for bacteria from an infected heart valve or traumatic site and splenic abscess may ensue. Diagnosis is made by noting the abscess on cross-sectioned imaging or observing a defect on liver–spleen scan performed for persistent infection. Splenic abscess is treated by splenectomy.

Aneurysms of the arterial blood supply to the spleen may rupture and require splenectomy. Rupture, however, is too rare a complication to produce a uniform recommendation for prophylactic splenectomy. Women having a splenic artery aneurysm and contemplating pregnancy should be advised of the increased risk of rupture during pregnancy.

## TECHNIQUES OF SPLENECTOMY

The spleen may be removed by open surgery or by a laparoscopic technique. In both techniques, the separation of the greater curvature of the stomach from the splenic flexure of the colon occurs by dividing the fatty tissue in the gastrocolic omentum. As the dissection is carried cephalad along the greater curvature of the stomach, the greater curvature may be brought forward and folded upward to expose the splenic artery originating from the celiac axis; the short gastric vessels are seen and divided high on the greater curvature. In operations performed for low platelet counts (e.g., ITP), the splenic artery may be secured on visualization, allowing platelet transfusion before division of the remaining vessels and mobilization of the spleen.

## STAGING OF HODGKIN'S DISEASE

The spleen is sometimes involved with malignant lymphoma. Operative removal of the spleen, liver biopsy, and lymph node sampling were commonplace before computed tomography and lymphangiogram were shown to accurately stage Hodgkin's disease in most cases. Such "staging laparotomy" is now reserved for individuals with equivocal imaging where differences in treatment result from knowing whether or not the spleen is involved.

## COMPLICATIONS OF SPLENECTOMY

Removal of the spleen may be accompanied by bleeding. This may be from a named vessel or from surgical division of splenic capsular adhesions to the abdominal side wall or diaphragm. Thrombocytopenic conditions increase the likelihood of bleeding from such sites.

Damage to the pancreatic tail during splenectomy may result in pseudocyst formation as pancreatic ductal integrity is lost and the fibroblastic containment is incomplete. When the pancreatic tail is thought to have been potentially injured during splenectomy, a drain is left in the splenic fossa; high amylase levels from the drainage effluent suggest that the drain be retained. The resultant pancreaticocutaneous fistula will often close without surgery. Left subphrenic abscess from superinfection of blood or pseudocyst contents may require radiologic or open drainage. Howell-Jolly bodies (nucleated red cells) and thrombocytosis (sometimes to greater than 1,000,000 platelets per cubic centimeter) may occur following splenectomy. Antibody production by the spleen stops with splenectomy, with a concomitant decrease in opsonization of encapsulated bacteria.

Overwhelming postsplenectomy sepsis represents the end result of a predisposition to infection with pneumococcus, meningococcus, and *Haemophilus influenza* bacteria as a consequence of splenectomy. Most fatalities occur in children and concerns for the development of postsplenectomy sepsis have prompted some to recommend long-term penicillin therapy following splenic removal in the pediatric population. In the adult population, increased awareness of the potential for infection and lower threshold for antibiotic treatment of upper respiratory infections are suggested in postsplenectomy patients.

In most cases of elective splenectomy, the operation is preceded by vaccination for the encapsulated organisms; the resultant antibodies may be at least transiently protective.

### See Also the Following Article

Laparoscopy

### Further Reading

Asknes, J., Adelnour, M., and Mathisen, O. (1995). Risk factor associated with mortality and morbidity after elective splenectomy. *Eur. J. Surg.* 161, 253–258.

George, J., El-Harake, M., and Raskob, G. (1994). Chronic idiopathic thrombocytopenic purpura. *N. Engl. J. Med.* 331, 1207–1211.

Lambert, C., and Williamson, J. (1990). Splenic artery aneurysm: A rare case of upper gastrointestinal bleeding. *Am. Surg.* 56, 543.

# Stents

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**ampulla of Vater** The aperture surrounded by the sphincter of Oddi.

**sphincter of Oddi** Circular muscle located at the aperture where common bile duct and pancreatic ducts join the duodenum.

**T-tube** Synthetic tube in the shape of a "T" whose transverse limb stents the site of an incision in the bile duct and whose vertical limb is brought through that incision and through the abdominal wall. Biliary anatomy may be defined by the injection of contrast material through the vertical arm and stones may be manipulated through it.

**A stent is a tubular prosthesis introduced into a hollow viscus to ensure that the viscus retains a minimum functional diameter despite obstruction occasioned by occlusion of the visceral lumen by stone, tumor, or extrinsic compression. Stents may be used temporarily in situations in which resolution of the obstruction is likely to occur or to ensure minimal visceral diameter in diverse processes (e.g., cancer) wherein the compromise of visceral diameter is anticipated to be permanent or progressive. Typical sites for visceral stent placement in decreasing order of frequency are the biliary tree, the esophagus, the pancreatic duct, and the sigmoid colon. Neoplastic disease of gastrointestinal origin may occasionally lead to permanent placement of stents in the ureter(s) to permit continued passage of urine from the upper urinary tracts to the bladder. Some surgeons use temporary ureteral stents as a means of palpably identifying the ureters during operations on the sigmoid colon.**

Stents (named for a 19th century dentist, Dr. William Stent) are typically introduced under endoscopic or fluoroscopic guidance and placed in a position where the prosthesis will allow normal passage of food or secretions through the narrowed segment because both of its ends are in undiseased or unobstructed regions of the viscus (Fig. 1). Visceral stents may be solid or webbed and are typically fashioned of plastic or metal.

## THE BILE DUCT

The unobstructed biliary tree is "self-flushing" by the four cooperative processes of ongoing bile production, relaxation of the sphincter of Oddi with meal ingestion, propulsion of bile by gallbladder contraction, and intrinsic peristalsis of the biliary tree. Stasis of bile behind malignant strictures, benign strictures, or stones predisposes to cholangitis, as indigenous bacteria, failing to be expelled into the gut, proliferate. This may lead to local or systemic infection. Instrumentation of the biliary tree endoscopically or transhepatically may introduce exogenous bacteria into an obstructed system as an unwanted by-product of therapy.

### Biliary Obstruction Secondary to Stone Disease

The endoscopic release of biliary obstruction due to stones involves retrograde manipulation of the biliary tree and extraction of stones through the ampulla of

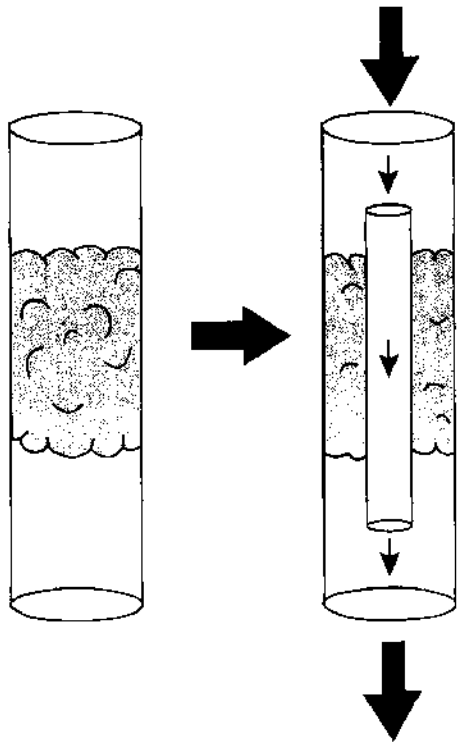

FIGURE 1 A stent traverses an area of obstruction, permitting flow through it. The ends of the stent are in normal areas of the obstructed organ.

 

Vater; an operating endoscope traverses the mouth, pharynx, esophagus, and stomach to reach the duodenum. Endoscopic access to the ampulla for stone extraction and biliary drainage is facilitated by enlargement of the ampulla of Vater by cutting the surrounding sphincter of Oddi (cf. sphincterotomy). Confidence that swelling or a retained stone would not result in cholangitis from endogenous or introduced bacteria is enhanced by the introduction of temporary stents through the endoscope to span the ampulla at the end of the extraction procedure. One end of such a stent rests in the bile duct and the other rests in the duodenum. As with T-tubes left in the bile duct after surgical manipulation, stents are typically removed when stones are documented to be absent on a subsequent radiologic study and/or when swelling from the manipulation of sphincterotomy has subsided and free drainage of bile from the duct can be documented.

### Biliary Obstruction Secondary to Pancreatitis

The most common reason for extrinsic compression of the bile duct is inflammation or injury of the pancreatic head, with resultant swelling of the ampulla. Such swelling can cause derangement of liver function tests similar to that seen in obstructing stone or tumor. Diagnostic endoscopic retrograde cholangiopancreatogram (ERCP) with therapeutic stenting of a bile duct obstructed from pancreatitis may exclude stones as the cause of the inflammation and normalize elevated levels of alkaline phosphatase, transaminases, total bilirubin, and conjugated bilirubin. Treatment of the pancreatitis itself is supportive (cf. pancreatitis) and some such structures resolve with the resolution of the inflammation.

### Malignant Obstruction of the Biliary Tree and Esophagus

Malignant obstruction of the common bile duct secondary to neoplasm of the distal bile duct, ampulla of Vater, or pancreatic head produces elevation of liver function tests. ERCP shows neither a silhouetted stone in transit nor the smooth stricture of pancreatitis, but an abrupt end of both pancreatic and bile ducts in the region of the ampulla (the so-called double duct sign). Endoscopic manipulation of the ampulla for diagnostic cytology or retrograde injection of the contrast to define the anatomy during ERCP may introduce bacteria into an obstructed system. Stent placement may allow normalization of liver function tests in anticipation of an operation performed to resect or bypass the neoplasm with curative or palliative intent. Alternatively, in patients at high risk or with metastatic disease, stent placement is intended to be permanent and to provide a palliative alternative to open surgery. Because of the stent's small caliber and resultant tendency to obstruct with biliary debris, endoscopic replacement is often required or performed prophylactically at 3-month intervals.

With esophageal malignancies, lifetime stenting is considered as an alternative to surgery because a majority of patients subjected to "curative" surgery for malignant stricture in this region do not survive 5 years.

## STENTING OF THE PANCREAS

Repeated bouts of alcoholic pancreatitis produce segmental stricturing of the pancreatic duct with stone formation and pain. ERCP defines whether the fibrotic ductal changes as the gland heals are obliterative or obstructive. Surgical decompression of the duct with longitudinal pancreaticojejunostomy (Puestow procedure) or ablative procedures of the tail [distal pancreatectomy or retrograde drainage of the pancreatic duct (the Duval procedure)] have wide variation in success of relieving pain and allowing withdrawal of narcotics depending on whether the pain is due to obstruction or inflammation. Interventional failures may be multifactorial in this population. Alcoholic recidivism may cause painful recurrent attacks of acute pancreatitis.

Permanent stenting of the pancreatic duct as an alternative to surgery to relieve the pain of chronic obstruction is controversial, as the small caliber of the stents requires frequent changes for occlusion. Some have suggested stents as a predictive tool to define who would benefit from a surgical decompressive approach and traverse the obstruction in the pancreatic duct. Such stents are introduced through the ampulla during ERCP. The absence of relief from stenting predicts a minimal impact of surgical duct decompression on narcotic requirements.

## STENTING OF THE COLON

Placement of a stent in the sigmoid colon to facilitate bowel preparation for an obstructing cancer or as an alternative to surgical resection or diversion is controversial. Placed retrograde through a colonoscope, the prosthesis clogs easily with solid fecal material indigenous to the left colon; it may also dislodge, erode, cause bleeding, or pass with the stool. The use of stents to ensure a minimal diameter for the sigmoid colon competes unfavorably with surgery; even with metastatic disease, most patients with sigmoid colon cancer can be surgically resected or diverted. Few patients able to

have sigmoid resection are so obstructed that no mechanical preparation of the bowel can be carried out. Intraoperative alternatives to stenting, such as on-the-table bowel irrigation, further limit the role of stenting.

## STENTING AS AN ADJUNCT TO SURGERY

When surgical resection or bypass involves anastomosis of a small duct, such as the pancreatic duct or bile duct, to the small intestine, some surgeons advocate temporary stents to ensure a guaranteed anastomotic diameter, thereby ensuring patency and facilitating drainage as anastomoses heal. The absence of controlled studies makes it impossible to determine whether such an approach is beneficial; for larger anastomoses (e.g., of ducts enlarged by chronic obstruction), most surgeons do not use such a prosthesis.

## URETERAL STENTS AND THE GASTROINTESTINAL TRACT

Ureteral stents are used in association with treatment of gastrointestinal disease in two circumstances: to identify and preserve ureters during operations on the gastrointestinal tract in which such identification might be difficult and to ensure renal function in obstructing pelvic cancers.

Stents placed to avoid ureteral injury are introduced through retrograde cystoscopic cannulation of the ureteral orifices with rigid tubes. In operations on the lower gastrointestinal tract (e.g., sigmoid colon for diverticulitis or malignant disease), such identification is said to help some surgeons avoid injury.

For advanced pelvic malignancy, the need for stents is often identified by alteration in renal function or demonstration of distal ureteral obstruction on a radiographic study such as ultrasound or computed tomography. Stenting is preferable to anuria in circumstances in which a therapeutic impact on the obstructing malignancy is likely. When obstructing malignancy is unlikely to be able to be successfully treated, ureteral obstruction may be left unstented, as the toxicity of renal failure occasions a death preferable to that of a painfully growing untreatable pelvic malignancy. When chronic ureteral stenting is used, stent changes are often required because of debris collection in the small-lumen tubes.

### See Also the Following Articles

**Bile Duct Injuries and Fistulas • Sphincterotomy**

### Further Reading

Assimus, D. G., Patterson, L. C., and Taylor, C. L. (1994). Changing incidence and etiology of iatrogenic ureteral injuries. *J. Urol.* 152, 2240–2246.

Carr-Locke, D. (1999). Endoscopic therapy of chronic pancreatitis. *Gastrointest. Endosc.* 49, 577–580.

Ho, H. S., and Frey, C. (1997). Current approaches to the surgical management of chronic pancreatitis. *The Gastroenterologist* 5, 128–136.

Savage, P. T. (1967). Immediate resection with end-to-end anastomosis for carcinoma of the large bowel presenting with acute obstruction. *Proc. R. Soc. Med.* 60, 207–209.

Stear, M., Waxman, I., and Freedman, S. (1995). Chronic pancreatitis. *N. Engl. J. Med.* 332, 1482–1490.

# Stomach, Adenomas and Carcinomas of the

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**acanthosis nigricans** Darkly pigmented velvety patches of skin folds found in association with gastrointestinal malignancies.

**chromoendoscopy** Spraying of a dye that can be seen endoscopically and that may highlight surface irregularities or specific histologic features.

**dermatomyositis** Inflammatory myopathy manifested by symmetric proximal muscle weakness and skin rash, often in association with malignancies.

**endoscopic ultrasound (endosonography)** Use of an ultrasound transducer at the endoscope tip to obtain sonographic images of anatomic structures adjacent to the endoscope.

**incidence** Number of new cases of a specific disease found in a defined population over a specific time period (such as the number of new cases over a 1-year period).

**Leser–Trelat sign** Sudden appearance of multiple seborrheic keratoses, often concomitant with acanthosis nigricans, found in association with gastrointestinal malignancies.

**premalignant polyp** Cell growth that has the potential of progressing to a malignancy over time.

**prevalence** Number of existing cases of a specific disease found in a defined population at one specific point in time.

**Trousseau's syndrome** Migratory superficial thrombophlebitis occurring as a result of a hypercoagulable state, often in association with or preceding the diagnosis of cancer.

Gastric polyps are nonmalignant, protruding, intraluminal masses inside the stomach, found in 1–2% of patients. Adenomas account for about 10% of gastric polyps. Adenomas are premalignant polyps, and are believed to progress to malignant gastric neoplasms over time. Nonadenomatous polyps generally have no documented malignant potential (with the possible exception of gastric fundic polyps in patients with familial adenomatous polyposis). Gastric carcinomas (also called gastric cancers), or adenocarcinomas of the stomach, include carcinomas in the cardia, which also involve the esophagogastric junction. They do not include squamous cell carcinomas (almost universally with an esophageal primary) involving the esophagogastric junction. Carcinomas of the stomach account for about 90% of all malignant gastric neoplasms, which also include lymphomas, stromal cell tumors, and carcinoids.

## ADENOMAS OF THE STOMACH

Adenomas of the stomach are found throughout the stomach, but are more common in the antrum and along anastomoses. They are variable in size, ranging from a few millimeters to several centimeters in diameter. They are true premalignant gastric polyps. Their malignant potential increases with increasing size, increasing villous component, higher degree of dysplasia, and multiplicity in number. In adenomas larger than 2 cm, there is about a 10% frequency of carcinoma within the adenoma.

Although there have been no large-scale prospective studies, some reports suggest an association of gastric adenomas with colon adenomatous polyps. Patients with gastric adenomas may have a fourfold higher risk of having colon adenomatous polyps, and those with colon adenomatous polyps may have up to a 20-fold increase in gastric adenomas. A special clinical setting involves the patient with familial adenomatous polyposis. These patients often have multiple fundic gland polyps. Sporadic fundic gland polyps in patients without familial adenomatous polyposis appear to have no malignant potential. However, in patients with familial adenomatous polyposis, their fundic gland polyps may be pathogenetically distinct from sporadic fundic gland polyps, carry genetic alterations, and have malignant potential. In patients with familial adenomatous polyposis, polypectomy or biopsies of multiple fundic gland polyps are needed to detect adenomatous or malignant changes. In addition, because of the increased frequency of gastroduodenal cancers in such patients, periodic surveillance endoscopy is indicated.

Small gastric adenomas less than 1 cm in size, like most other small gastric polyps, are usually asymptomatic. But larger adenomas, because of their propensity to be located in the antrum, may cause gastric outlet obstruction, epigastric distress or pain, as well as occult or overt bleeding. With the wide use of endoscopy examinations, most gastric adenomas are diagnosed during endoscopic examinations, usually for abdominal pain or occult blood loss. When found, all gastric polyps should be excised totally by polypectomy if feasible. If total

excision is not possible, a focus of invasive carcinoma could very well be missed. For multiple gastric polyps, the largest five or six should be removed totally by polypectomy, followed by biopsy of a representative sample of the remainder. For adenomas larger than 2 cm, endoscopic ultrasound may be helpful in determining which layers of the stomach wall are involved. If invasive carcinoma is found or if there are multiple large gastric adenomas, a subtotal gastrectomy might be indicated. Once gastric adenomas are found, the patient probably should have a surveillance endoscopy at 1 year. If there is recurrence of adenomatous polyps or if adenomatous tissue is present on biopsy, surveillance endoscopy 1 year later is again indicated. If the repeat examination at 1 year is negative, the next endoscopy could be delayed for 3 to 5 years, analogous to the current recommendation for the surveillance of colon adenomatous polyps. No surveillance is indicated if the gastric polyp is nonadenomatous.

Several small-scale studies suggest that *Helicobacter* eradication may lead to regression of gastric adenomas and delay or inhibit their progression to cancer. Eradication of *Helicobacter* in patients with gastric adenomas and concomitant *Helicobacter* infection would appear warranted.

## CARCINOMAS OF THE STOMACH

### Introduction

In the United States, carcinoma of the stomach is the eleventh most common type of cancer and is the fourteenth leading cause of cancer death. For the year 2003, 22,400 new cases of, and 12,100 deaths from, carcinoma of the stomach were projected. Worldwide, carcinoma of the stomach remains the second most common cancer and the second most common cause of cancer death, despite a continuing worldwide decline in prevalence and death rate over the past seven decades. Even with the decline in the overall incidence of carcinomas of the stomach, the decline is primarily that of carcinomas in the distal stomach; whereas the incidence of carcinomas in the gastric cardia has been increasing rapidly in the past three decades. This appears to be accounted for primarily by an increase in carcinomas associated with Barrett's esophagus.

Worldwide, there is also a 10-fold or greater difference in the incidence and prevalence of carcinomas of the stomach, with the highest incidence in Japan, Korea, China, and eastern Europe, and the lowest incidence in North America, western Europe, Australia, and New Zealand. Even within the same country, incidence can be markedly variable. For example, there is a high incidence in the mountainous regions of Columbia, but not in the coastal regions. This regional difference has been attributed to environmental factors. Japanese immigrants in the United States have about a 25% reduction in incidence of gastric carcinomas compared to the general Japanese population. The second generation has more than a 50% reduction, and subsequent generations have an incidence comparable with that of the general United States population.

### Etiology and Risk Factors

The pathogenesis of carcinomas of the stomach is most likely multifactorial. There has long been postulated a sequence of histologic premalignant changes, progressing from atrophic gastritis to intestinal metaplasia and ultimately to carcinoma. These premalignant histologic changes may be necessary but clearly are not sufficient. The existence of a genetic predisposition is suggested by the finding of carcinoma of the stomach in patients with Lynch syndrome II, one of the hereditary nonpolyposis colorectal cancer syndromes. Many patients with familial adenomatous polyposis also develop adenomas and carcinomas of the stomach. In addition, studies have shown an approximately twofold increase in the relative risk of carcinomas of the stomach in twins and in first-degree relatives of patients with gastric carcinomas.

Currently, it appears that the most clinically significant risk factor is *Helicobacter pylori* infection. Patients with *Helicobacter* infection have a three- to eight-fold increased risk of developing carcinomas of the stomach. The exact pathogenetic mechanisms have not been defined. With the increasingly frequent detection of *Helicobacter* infection, specifically in association with peptic ulcer disease, there is ongoing use of antibiotics to eradicate chronic *Helicobacter* infections in developed countries. This may eventually help fuel further declines in the prevalence and incidence of carcinomas of the stomach.

Many other risk factors have also been proposed for carcinomas of the stomach. However, most of these other risk factors have been associated with only small and inconsistent increased risks. The strongest risk factors, other than heredity and *Helicobacter* infection, include pernicious anemia, previous gastrectomy or gastric surgery, chronic atrophic gastritis, and intestinal metaplasia.

### Clinical Manifestations

The clinical presentation of carcinomas of the stomach is dramatically different in Japan compared to the rest of the world. Japan has very high incidence and has had a

national screening program in place since the 1960s. Perhaps as a result of the aggressive screening program, carcinomas of the stomach tend to be at an early stage when diagnosed in Japan. Early gastric cancer, defined as carcinoma limited to only the mucosa and submucosa, accounts for up to 50% of cases of gastric carcinomas in Japan. However, early gastric cancer accounts for fewer than 20% of cases in the United States.

Early gastric cancer tends to be asymptomatic in up to 80% of patients. In advanced gastric carcinoma, i.e., in patients with later stage disease, the most common findings are weight loss and abdominal pain. In addition, nausea and vomiting, anorexia, dysphagia, occult or overt gastrointestinal blood loss, early satiety, and symptoms of peptic ulcer disease are found in more than one-quarter of patients. All of these symptoms are, of course, nonspecific. In addition, advanced gastric carcinomas may also present with nodal metastases and intraabdominal metastases, and their associated signs and symptoms, including adenopathy, ascites, and gastrointestinal obstruction. Paraneoplastic conditions, such as Trousseau's syndrome, acanthosis nigricans, Leser–Trelat sign, and dermatomyositis, have been described.

## Diagnosis

The diagnosis of carcinoma of the stomach is best made by endoscopy with biopsy. The endoscopic appearance of carcinomas can range from polypoid masses, often with ulcerations, to ulcerating masses, and to superficial and infiltrating lesions. Both early and advanced carcinomas have been classified morphologically, but the morphologic classifications have limited clinical value for staging, treatment, or prognosis.

Definitive tissue diagnosis requires endoscopic biopsy. Diagnostic accuracy is highest when at least six biopsies are taken. If an ulcer is present, biopsies should be taken from the edge and base of the ulcer and not from the necrotic debris. Chromoendoscopy with dye staining may help highlight suspicious areas to guide targeted biopsy. Contrast radiological studies may be used for diagnosis, but a followup endoscopic examination with biopsy is still indicated to confirm tissue diagnosis and guide subsequent treatment and management.

Imaging studies may also be helpful in staging. Computed tomography (CT) scans are especially helpful in detecting pulmonary or hepatic metastases, as well as intraabdominal and large peritoneal metastases. CT scans often underestimate the size and extent of involvement of the primary tumor and can miss small intraabdominal and peritoneal metastases of 5 mm or less, and are therefore prone to understaging. Endoscopic ultrasound is most helpful for defining the extent of the primary tumor. It can have up to 90% accuracy in defining the depth of invasion, and this is especially helpful in differentiating early gastric cancer from more advanced disease. Endoscopic ultrasound is also helpful in detecting perigastric lymph node involvement. In addition, endoscopic ultrasound-guided fine needle aspiration can enhance staging accuracy. However, distant lymph nodes, the liver, and the lungs cannot be imaged satisfactorily. In patients who present higher surgical risks, some surgeons also prefer preoperative laparoscopy to detect small peritoneal metastases and to determine surgical resectability.

## Screening

Japan is the only country that has published results of large nationwide population screening programs for carcinomas of the stomach. Screening was initially by double-contrast radiographs, then by intragastric cameras, but is now done totally by endoscopy. About 7 million persons are screened and about 7000 cases of carcinomas of the stomach are identified annually. This accounts for more than 100 cases per 100,000 persons screened. More than 50% of gastric carcinomas detected by screening are early gastric cancers. About 90% have no lymph node involvement, undergo curative resection, and have 5- and 10-year survival rates of greater than 90%. Further analysis shows that persons undergoing screening have 50% lower risks of dying from carcinomas of the stomach compared to those who do not participate in screening.

In the rest of the world, including the United States, the incidence of carcinomas of the stomach is markedly lower and renders screening less clinically effective and thus much less cost-effective. In the United States, even in persons with identified predisposing risk factors, such as *Helicobacter* infection, pernicious anemia, previous gastrectomy, chronic atrophic gastritis, and intestinal metaplasia, screening does not appear to have value. Although there are no published data or clinical trials, relative risk data suggest that screening can be recommended only for patients with identified adenomas of the stomach, as well as those with familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer.

## Staging

The most important factor in determining the curative resectability and prognosis of carcinomas of the stomach is clinical stage. There are minor differences in the staging systems currently in use, but most systems are comparable. Most generally accepted staging

systems are based on the primary tumor (T), nodal involvement (N), and metastasis (M) (TNM) system, whereby these factors are used to determine a clinical stage. Patients with carcinoma (tumor) *in situ* (Tis) or intraepithelial neoplasia have stage 0 disease, and have a chance of 5-year survival of close to 100%. Those with T1 tumors, limited to the mucosa and submucosa (also termed early gastric cancer), are generally stage I, and have 5-year survival rates of higher than 90%. T2 tumors, with involvement of the muscularis propria, generally fall into stages II and III, and patients have 5-year survival rates of about 50%. Patients with T3 tumors, which involve the serosa and are generally stage III, have 5-year survival rates of about 20%. Patients with T4 tumors, which involve adjacent organs and structures, almost always have nodal involvement or distant metastases. They usually have stage IV disease and have virtually a 0% 5-year survival rate (Figs. 1 and 2).

## Treatment

Surgical resection of the primary carcinoma and excision of adjacent involved lymph nodes remain the standard of treatment. Even with advanced disease that is not amenable for cure, surgical resection with palliative intent remains the most effective way of providing symptomatic relief, with relief of abdominal pain and obstructive symptoms in more than 50% of patients. Therefore, laparotomy or laparoscopy with curative intent and to optimize palliation should be carried out in virtually all patients except those who are not surgical candidates or those with advanced distant metastases and no local obstructive symptoms. For patients with polypoid early gastric cancers, Japanese endoscopists will perform endoscopic mucosal resection, although this technique has not seen wide use in the United States. For those patients not amenable to surgical resection or palliation, or for those in whom surgical palliation is not possible, endoscopic balloon dilation, stent placement, thermal therapy, laser therapy, or photodynamic therapy can provide palliation in selected patients.

The high recurrence and relapse rates after curative and palliative resections have prompted numerous studies on preoperative and postoperative adjuvant therapy. So far, there is no evidence that preoperative adjuvant radiation therapy or chemotherapy has any survival benefit. Similarly, postoperative radiation therapy has also not shown any survival benefit. Postoperative adjuvant therapy, as well as chemotherapy for advanced nonresectable disease, has shown a small survival benefit. More than 30 chemotherapeutic agents, used as single agents or in combination, have been tested in clinical trials. Successful single-agent or combination chemotherapy regimens have shown about a 30% response rate, almost always partial responses, but no or only limited survival benefit. The current standard

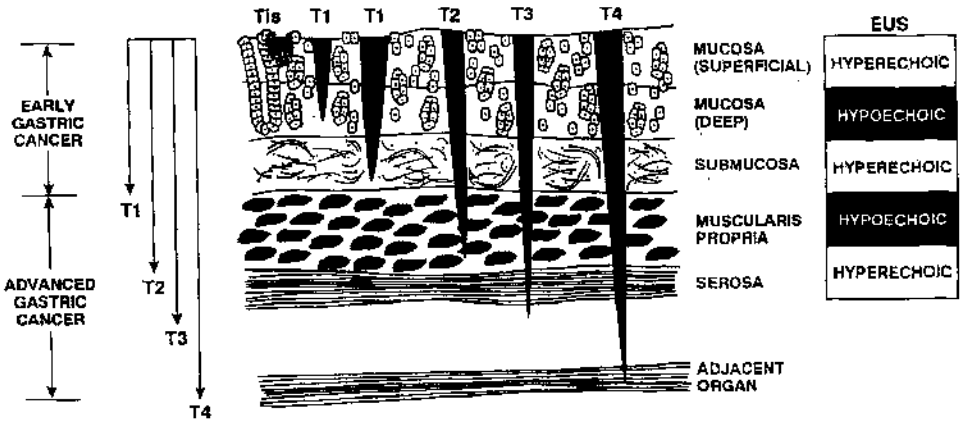
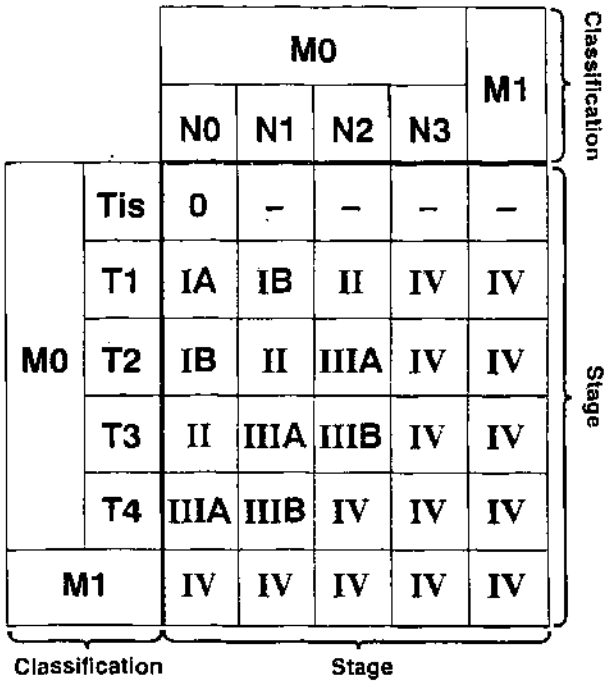



FIGURE 1 Classification of gastric carcinomas by depth of primary tumor invasion (T classification). In the tumor/node/metastasis (TNM) classification, T denotes depth of invasion. Tis designates carcinoma (tumor) *in situ* (intraepithelial neoplasia); T1 tumors are confined to the mucosa and submucosa, T2 tumors penetrate the muscularis propria but not the serosa, T3 tumors penetrate the serosa without involving contiguous structures, and T4 tumors penetrate the serosa and involve adjacent organs and tissues. In early gastric cancer, the disease is confined to the mucosa and submucosa, without regard to size or nodal involvement, and is equivalent to T1 tumors. The layers of the gastric wall may be visualized by endoscopic ultrasound (EUS) as five layers, alternately hyperechoic (bright) and hypoechoic (dark). Reproduced with permission from Figure Luk, G. D. (1998). Tumors of the stomach. *In* "Gastrointestinal and Liver Disease" (M. Feldman, B. F. Scharschmidt, and M. H. Sleisenger, eds.) 6th edition, page 743. Copyright W. B. Saunders.




| Stage | 5-Year Survival |
|---|---|
| 0 | 100% |
| IA | 95% |
| IB | 82% |
| II | 55% |
| IIIA | 30% |
| IIIB | 15% |
| IV | 2% |
| EGC (T1) | 90% |

**FIGURE 2** Tumor/nodule/metastasis (TNM) staging of gastric carcinoma and relationship to survival. This common staging system is based on the TNM classification. T classification is by depth of primary tumor invasion (see Fig. 1), and N classification is by nodal involvement: N0 represents no nodal involvement, N1 represents involvement of perigastric nodes within 3 cm of the primary tumor, N2 represents involvement of more distant perigastric nodes and regional nodes that are amenable to removal at gastrectomy, and N3 represents involvement of more distant intraabdominal nodes that are not removable at surgery. Stage 0 represents Tis, carcinoma (tumor) *in situ*, which is not a true clinical malignancy. Stage IA represents the earliest stage of malignancy, progressively advancing through stages IB, II, IIIA, IIIB, and finally stage IV. Stage IV represents disseminated metastatic disease, with the presence of M1 at any T or N stage. Although it is theoretically possible to have stage IV disease that is T1N0M1, most stage IV disease is T3 or T4 with at least N2 involvement. It is also important to note that early gastric cancer, which is T1 disease, may be a separate clinical entity with a highly favorable prognosis and for which gastrectomy is curative, at least in Japan. Reproduced with permission from Figure Luk, G. D. (1998). Tumors of the stomach. *In* "Gastrointestinal and Liver Disease" (M. Feldman, B. F. Scharschmidt, and M. H. Sleisenger, eds.) 6th Ed., p. 744. Copyright W. B. Saunders.

combination regimen is that of epirubicin, cisplatin, and fluorouracil (ECF). This has been shown to have about a 50% response rate, with a few complete responses, and to confer about a 3-month survival advantage. For patients who cannot tolerate or have failed standard therapy, there are generally ongoing clinical trials sponsored by The National Cancer Institute, and patients who meet eligibility criteria may benefit by being enrolled in these clinical trials. It appears that most new advances in the early detection and management of adenomas and carcinomas of the stomach will emanate from Japan, where the disease is much more prevalent and where there are well-established national screening and research programs.

## See Also the Following Articles

**Atrophic Gastritis • Cancer, Overview • Familial Adenomatous Polyposis (FAP) • Gastrectomy • Gastric Cancer Surveillance • Gastric Polyps • Gastric Surgery • *Helicobacter pylori* • Pernicious Anemia**

## Further Reading

Abraham, S. C., Nobukawa, B., Giardiello, F. M., Hamilton, S. R., and Wu, T. T. (2000). Fundic gland polyps in familial adenomatous polyposis: Neoplasms with frequent somatic adenomatous polyposis coli gene alterations. *Am. J. Pathol.* 157, 747–754.

American Cancer Society. (2003). Stomach cancer web site: http://www.cancer.org/docroot/home/index.asp.

Archimandritis, A., Spiliadis, C., Tzivras, M., Vamvakousis, B., Davaris, P., Manika, Z., and Scandalis, N. (1996). Gastric epithelial polyps: A retrospective endoscopic study of 12974 symptomatic patients. *Ital. J. Gastroenterol.* 28, 387–390.

Boland, C. R., and Savides, T. J. (1999). Tumors of the stomach. *In* "Textbook of Gastroenterology" (T. Yamada, D. H. Alpers, C. Owyang, L. Laine, and D. W. Powell, eds.), 3rd Ed., pp. 1500–1529. Lippincott Williams & Wilkins, Philadelphia.

Coulon, K. C., and Brennan, M. F. (2000). Laparoscopy for staging abdominal malignancies. *Adv. Surg.* 34, 331–350.

De Vivo, R., Pignata, S., Palaia, R., Parisi, V., and Daniele, B. (2000). The role of chemotherapy in the management of gastric cancer. *J. Clin. Gastroenterol.* 30, 364–371.

Greenlee, R. T., Hill-Harmon, M. B., Murray, T., and Thun, M. (2001). Cancer statistics 2001. *CA Cancer J. Clin.* 51, 15–36.

Luk, G. D. (1998). Tumors of the stomach. *In* "Gastrointestinal and Liver Disease" (M. Feldman, B. F. Scharschmidt, and M. H. Sleisenger, eds.). 6th Ed., pp 733–757. W. B. Saunders, Philadelphia.

National Cancer Institute. (2003). NCI CancerNet web sites: Stomach (Gastric) Cancer, http://cancernet.nci.nih.gov/Cancer_Types/Stomach_(Gastric)_Cancer.shtml; What You Need to Know about Stomach Cancer, http://cancernet.nci.nih.gov/wyntk_pubs/stomach.htm; NCI Clinical Trials, News and Search, http://cancertrials.nci.nih.gov/index.html.

National Institutes of Health (2003). NIH Medline Plus stomach cancer web site: http://www.nlm.nih.gov/medlineplus/stomachcancer.html.

Saito, K., Arai, K., Mori, M., Kobayashi, R., and Ohki, I (2000). Effect of *Helicobacter pylori* eradication on malignant transformation of gastric adenoma. *Gastrointest. Endosc.* 52, 27–32.

Yoshikane, H., Sakakibara, A., Hidano, H., Niwa, Y., Goto, H., and Yokoi, T. (2001). Piecemeal endoscopic aspiration mucosectomy for large superficial intramucosal tumors of the stomach. *Endoscopy* 33, 795–799.

# Stomach, Anatomy

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**hiatal hernia** Protrusion of part of the stomach, usually the cardia, into the thoracic cavity through the esophageal opening of the diaphragm.

**mesothelium** A layer of cells lining an internal cavity of the body, such as the peritoneal or pericardial cavities.

**pepsin** A protein secreted in the stomach that begins cleaving ingested proteins into smaller polypeptides. It functions optimally in the acid environment of the stomach, at pH 1–3, and is inactivated when the acid is neutralized, at pH 5 or higher, in the duodenum.

**pernicious anemia** An anemic condition characterized by larger than normal (megaloblastic) red blood cells. Insufficient gastric production of intrinsic factor leads to deficient ileal absorption of vitamin B12. Deficiency of B12 leads to ineffective red blood cell production in the bone marrow.

**plexus** A network or joining together of multiple nerves, blood vessels, or lymphatic vessels.

**vagus nerve** Cranial nerve X. The paired vagus nerves provide parasympathetic innervation to the heart, lungs, and gastrointestinal tract to the level of the left colic flexure.

**The stomach is a distensible sac connected to the esophagus proximally and the duodenum distally. It serves two major functions in the digestive system. First, it is a temporary holding area for food, slowly portioning the mass of consumed food into the duodenum for further digestion and absorption. Second, food is mixed with gastric secretions and churned to be broken down into a semiliquid form, termed chyme. Both the gross anatomy and the microscopic anatomy of the stomach reflect these functions.**

## GROSS ANATOMY

### Location and Anatomic Divisions

The stomach is located in the left upper region of the abdomen, just beneath the diaphragm. Connected proximally to the esophagus and distally to the duodenum, the stomach is distensible, with a potential volume between 1200 and 3000 ml depending on the volume of food present. It is roughly shaped like the letter J; the medial concave side is known as the lesser curvature and the lateral convex side is known as the greater curvature (Fig. 1). The stomach can be divided into five parts. The

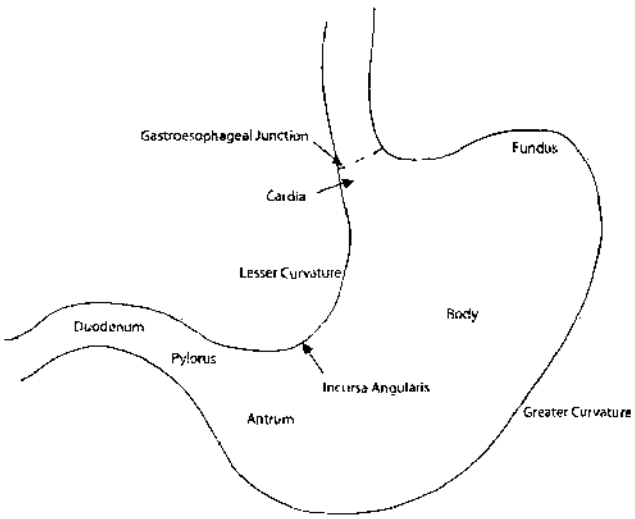


FIGURE 1 Anatomy of the stomach.

cardia is an ill-defined region beginning at the gastroesophageal junction and extending into the first to 2–3 cm of the stomach. The fundus is the section of stomach that lies superior to the gastroesophageal junction. Approximately two-thirds of the way along the lesser curvature lies a sharp angle known as the incisura angularis; above this angle to the level of gastroesophageal junction lies the corpus or body of the stomach. The distal third of the stomach, the antrum, extends below the incisura angularis. Finally, the pylorus is a narrow 1 to 2 cm long channel connecting the stomach to the duodenum. A relatively common alteration in gastric anatomy is a hiatal hernia. This condition increases the occurrence of esophageal reflux and may eventually lead to esophageal adenocarcinoma.

### Circulation

The stomach receives the majority of its blood supply from the celiac trunk, a branch off of the descending aorta that arises at the level of the T12 vertebra. The celiac trunk splits into three major divisions: the left gastric artery, the splenic artery, and the hepatic artery. The left gastric artery runs along the lesser curvature and anastamoses with the right gastric artery, a branch of the hepatic artery. The hepatic artery also gives rise to the gastroduodenal artery, which later becomes the right gastroepiploic artery. This artery runs along the greater curvature and supplies the lateral stomach, with two branches of the splenic artery, the left gastroepiploic and short gastric arteries. There are numerous interconnections, or anastamoses, among the arteries supplying the stomach, making ischemic infarction a very uncommon event.

### Innervation

The stomach receives both sympathetic and parasympathetic innervation. Sympathetic nerves arise from the thoracic spinal cord and synapse in the celiac ganglia. From there, the sympathetic nerves follow the gastric and gastroepiploic arteries to enter the stomach. Pain sensation from the stomach is relayed to the central nervous system by way of the afferent sympathetic fibers. Parasympathetic innervation comes from the vagus nerves. Both the paired anterior and posterior vagus nerves bifurcate as they enter the abdomen. The anterior vagus divides into the hepatic and anterior gastric branches and the posterior vagus forms the celiac and posterior gastric branches. The anterior and posterior gastric branches innervate the majority of the stomach, although the pylorus is innervated by the hepatic branch of the anterior vagus. In keeping with the "rest and digest" function of the parasympathetic nervous system, these nerves stimulate acid secretion in the body and fundus of the stomach and increase motility in the antrum.

## MICROSCOPIC ANATOMY

As in the rest of the gastrointestinal tract, the wall of the stomach is divided into four layers: mucosa, submucosa, muscularis propria, and serosa. These layers are specialized within the stomach to carry out the stomach's role in digestion.

### Mucosa

#### *General Appearance*

The mucosa is the innermost layer of the wall lining the stomach cavity. The mucosa and submucosa below it are piled into folds, known as rugae, in the contracted stomach. The rugae are haphazardly arranged in the fundus and body, but are arranged longitudinally in the antrum. As the stomach distends, the rugae flatten out to accommodate the increased volume.

On closer inspection, the mucosa consists of pits (foveolae) invaginating from the surface. Beneath these is an extensive network of glands that empty into the pits, with one to seven glands emptying into

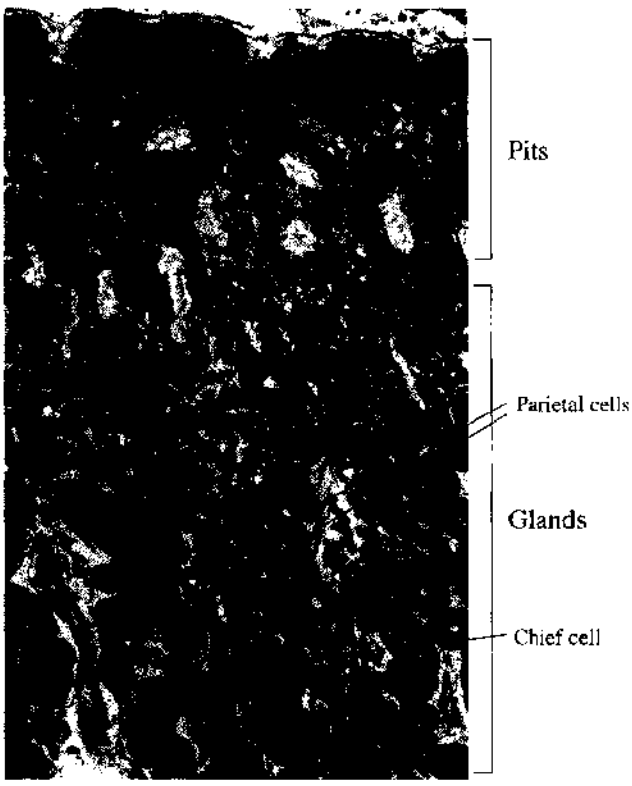


**FIGURE 2** Histology of the gastric body and fundus.

each pit (Fig. 2). Beginning at their entry into the pits, each gland is divided into an isthmus, a neck, and a base. The pits and glands are lined by a single layer of columnar epithelial cells. As described below, multiple specialized cells types that carry specific digestive functions are present in the gastric glands. The epithelial cells rest on the basement membrane, which separates the epithelial compartment of the mucosa from the lamina propria. The lamina propria is a loose collection of tissue that supports the epithelium; within it are blood vessels, nerves, lymphatic vessels, immune cells, and connective tissue. Together with the epithelium and the lamina propria, the final component of the mucosa is the muscularis mucosa. The muscularis mucosa is a continuous sheet of smooth muscle that defines the border between the mucosa and the submucosa. The muscularis mucosa is composed of two layers: an inner circular and an outer longitudinal layer.

The gastric mucosa is vital to the function of the stomach as a digestive organ. The epithelium is responsible for the secretion of substances important for digestion, including hydrochloric acid and pepsin. The lumenal pH of the stomach can be as low as 0.9–1.5. This harsh environment is important for the breakdown of food, but also potentially damaging for the lining of the stomach itself. Thus, the mucosa has several protective mechanisms that collaborate to form a barrier that protects the stomach from its own secretions. First, the cells that line that surface and pits secrete a thin layer of mucus that coats the epithelium and forms a barrier to acid diffusion. Additionally, active bicarbonate secretion by the surface epithelium creates a thin neutral pH environment at the epithelial surface. The cell–cell junctions that link gastric epithelial cells also form a barrier to acid movement, with the tight junctions preventing the leak of lumenal acid between epithelial cells. Loss of this barrier function is one of the first effects of nonsteroidal anti-inflammatory drugs, the most common cause of gastric injury in the United States. The rich gastric blood supply is important for the rapid clearance of leaked acid and as the principal source of oxygen and nutrients to the epithelium. Finally, the rapid turnover rate of the foveolar epithelium, which is replaced every 3–6 days, also ensures that any damage to the mucosa is repaired quickly. Given the harsh environment of the gastric lumen, all of these protective mechanisms are necessary for the prevention of serious mucosal damage. For example, decreased gastric blood flow, as in shock, or interruption of epithelial cell division, as occurs with some chemotherapeutic agents, can result in mucosal ulceration.

### *Body and Fundus*

These portions of the stomach mucosa are responsible for the majority of the secretions necessary for the stomach to function properly. As such, the glands form a thick layer that represents approximately three-quarters of the mucosal thickness. The remaining mucosa is devoted to the gastric pits. As is true throughout the stomach, the pits are lined by columnar cells that secrete mucus and bicarbonate.

The glands of the body and fundus contain several cell types. Parietal cells are the primary cells of these glands. These cells are distributed along the length of the gland, are roughly pyramidal in shape, and secrete hydrochloric acid and intrinsic factor. Intrinsic factor forms a complex with vitamin B12 in the gastric lumen and facilitates its adsorption in the distal ileum. Parietal cells (and chief cells, discussed below) are replaced only every 1 to 2 years, in contrast to every few days for the mucous cells. Thus, damage to parietal cells can lead to long-term problems; this is the case with pernicious anemia. Autoimmune destruction of parietal cells leads to a deficiency of intrinsic factor. Over a period of months to years, a shortfall in the level of vitamin B12 develops, leading to ineffective red blood cell production.

The parietal cells have a complex network of canals, or canaliculi, that run through them and open into the gland lumen. These canaliculi are lined with the $H^+$,$K^+$-ATPase, the proton pump responsible for acid secretion. These pumps are the target of a common class of therapeutic agents, the "proton pump inhibitors," that are used for the treatment of gastritis, gastric ulcer, and esophageal injury due to reflux of gastric acid. The proton pump is capable of creating a lumenal $H^+$ concentration 3 million times that found in the cell. Creating such a large gradient is energy-intensive. Thus, parietal cells contain abundant mitochondria, which are essential for the production of ATP. Secretion of acid and intrinsic factor from the parietal cell is stimulated by three different mediators. Vagus nerve stimulation leads to acid secretion, as does histamine release from nearby enterochromaffin-like (ECL) cells. In addition, gastrin released from G cells in the antrum also increases parietal cell secretions and stimulates increases in parietal cell mass.

Chief cells are predominantly confined to the bases of the gastric glands. These cells secrete pepsinogen I and II, the inactive precursors of pepsin. These precursors are cleaved in the low pH of the gastric lumen, at which point they become enzymatically active and are designated pepsin. The pepsinogens are packaged in granules that fill the cytoplasm of the chief cells; fusion

of the vesicle with the cell membrane leads to pepsinogen release. Stimulation via the vagus nerve is the primary activator of pepsinogen secretion.

An assortment of neuroendocrine cell types is also present in the gastric glands. In the body and fundic mucosa, most cells are ECL cells. These cells respond to G-cell-derived gastrin with the secretion of histamine, which, in turn, stimulates acid secretion. Serotonin-producing enterochromaffin cells are also present. Unlike the other cells of the mucosal glands, the endocrine cells secrete their products into the bloodstream within the lamina propria, rather than into the lumen of the gland. These hormones can then act on nearby (paracrine stimulation) or distant (endocrine stimulation) cells.

Mucous neck cells are also scattered within the glands and are most heavily clustered at the gland neck. These cells secrete some mucus, but their primary function is that of a stem cell. They divide to form undifferentiated daughter cells that are capable of several additional rounds of division before they differentiate into the various cell types that constitute the gastric epithelium. During differentiation, these cells migrate up to replace the surface mucous epithelium or migrate down to replace parietal, chief, and neuroendocrine cells.

### *Antrum*

The antrum is easily differentiated from the body and fundus on a microscopic level. This portion of the stomach does not have as great a secretory function as the body and fundus; thus, the antral glands occupy less than half of the mucosal thickness. The pits occupy the remaining majority of the mucosa. The pits are lined with mucus-producing cells similar to those cells found in the pits of the body and fundus. The glands of the antrum differ from those in the body and fundus, as they do not contain parietal or chief cells. Aside from mucus-producing cells and stem cells, endocrine cells dominate the antral glands. Approximately half of these endocrine cells are G cells, which produce gastrin. As mentioned earlier, gastrin is a hormone that stimulates parietal cells in the body and fundus to produce acid; it also enhances gastric motility. Significant numbers of serotonin-producing enterochromaffin cells and somatostatin-producing D cells also populate the antral glands.

## Submucosa

The submucosa is a layer of loose connective tissue located between the muscularis mucosa and the muscularis propria. Numerous plexuses of nerves, arteries, veins, and lymphatics are found in this layer.

## Muscularis Propria

The stomach differs from other parts of the digestive system in that its muscularis propria contains three distinct muscle layers instead of the usual two. The outer layer of longitudinally arranged fibers and the inner layer of circularly arranged fibers correspond to the two layers found throughout the rest of the digestive tract, but a third layer, consisting of obliquely arranged fibers, is located just interior to the circular layer. The muscularis propria of the stomach is also thicker than the muscularis propria throughout the remainder of the gastrointestinal tract. In addition to the important contractile function carried out by the muscularis propria, this thick muscle layer serves as an impediment to gastric ulcer progression. This is of critical importance, because the underlying serosa offers minimal protection and because ulcer extension through the muscularis propria leads to gastric perforation. The resulting spillage of gastric contents into the abdomen requires emergent surgery and is associated with a high rate of mortality.

At both the pylorus and the gastroesophageal junction, the circular layer is more pronounced, where it forms sphincters that allow the stomach cavity to be sealed off. Failure of the gastroesophageal junction can result in the reflux of gastric acid into the esophagus. Failure of the pylorus can result in unregulated release of incompletely processed food into the small intestine. Congenital hypertrophic pyloric stenosis, a disorder found more commonly in male infants, represents inappropriate expansion of the muscularis propria in the pyloric region with obstruction of the pyloric channel. Ingested food cannot enter the small intestine via the pylorus, resulting in projectile vomiting as the gastric contents are forced through the gastroesophageal junction. This condition is surgically correctable and is the most common surgery performed during the first 6 months of life.

## Serosa

The external, or peritoneal, surface of the stomach is covered by the serosa. This thin layer consists of loose connective tissue covered by a single layer of cuboidal mesothelial cells. This covering serves to reduce friction on the stomach during its churning movements.

## See Also the Following Articles

**Circulation, Overview • Duodenum, Anatomy • Esophagus, Anatomy • Gastrointestinal Matrix, Organization and Significance • Gastrointestinal Tract Anatomy, Overview • Pylorus**

## Further Reading

Gartner, L. P., and Hiatt, J. L. (1997). "Color Textbook of Histology." W. B. Saunders, Philadelphia, PA.

Gray, H. (1995). "Gray's Anatomy," 15th Ed. Barnes and Noble, New York.

Owen, D. A. (1997). Stomach. *In* "Histology for Pathologists" (S. Sternberg, ed.), 2nd Ed., pp. 481–493. Lippincott-Raven, Philadelphia, PA.

Raufman, J. P. (2003). Stomach: Anatomy and structural anomalies. *In* "Textbook of Gastroenterology" (T. Yamada, ed.), 4th Ed., pp. 1279–1291. J. B. Lippincott, Philadelphia, PA.

Turner, J. R., and Odze, R. D. Gastric polyps. *In* "Surgical Pathology of the Gastrointestinal Tract, Liver, Biliary Tract and Pancreas" (R. D. Odze, J. R. Goldblum, and J. M. Crawford, eds.). Harcourt Health Sciences, Baltimore, MD, in press.

# Stress

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**allostasis** Dynamic processes involved in the defense of homeostasis that are generated in response to real or perceived stressors/triggers.

**allostatic load** Cost of allostasis, which is the wear-and-tear damage resulting from chronic overactivity, underactivity, or mismanagement of allostatic systems, all of which can lead to disease and illness.

**homeostasis** Internal neurobiological stability and balance that are maintained through allostasis; critical to survival and health.

**stress** Adaptive physiological response to real or perceived threat to homeostasis; a natural system to protect and restore homeostasis, but can become harmful over time.

**stressor** External or internal physical, biological, environmental, or situational factors that represent an actual or perceived threat to homeostasis.

**The hormones and other physiologic agents that mediate the central stress response of the brain, body, and digestive system (gut) have protective and adaptive immediate effects that are essential for survival and maintenance of homeostasis and health (i.e., allostasis, or "good stress"). However, over longer time intervals, stress response agents exact a cost when they are over produced, under produced, or mismanaged (i.e., allostatic load, or "bad stress"). Alterations in the central stress response and allostatic load related to genetic, environmental, and behavioral influences contribute to the pathophysiology of a broad range of diseases and illnesses; however, scientifically validated strategies for reduction of harmful effects of the stress response and allostatic load are available.**

## INTRODUCTION

Many people with disease and illness note exacerbation of symptoms correlated with life events that are perceived to be stressful. Others fail to report any such association. What is stress and how common is it? How does the body respond to stress? Is stress good or bad for us? What can be done about stress? New scientific understanding of individual responses to acute and chronic stress and of the mind/brain–body/gut connection has resulted in a reassessment of the role of chronic stress in disease and illness.

## DISEASE AND ILLNESS

Disease can be defined as the externally verifiable evidence of a pathological state, whereas illness is defined as a person's perception of ill health, which is evident from symptom reports, beliefs, and behavior. There can be a significant discordance between disease and illness. For example, an individual with the disease of a deep peptic ulcer of the stomach or duodenum may not describe any illness symptoms, such as abdominal pain. By contrast, a person with a small and superficial ulcer may report severe pain. The stress response contributes to the pathophysiology of disease and illness and helps explain their common discordance.

## DEFINITION OF STRESS

Stress is an adaptive physiological response to the detection of either external (exteroceptive) or internal (interoceptive) stressors. Bruce S. McEwen developed a new way of conceptualizing and understanding the stress response (Fig. 1). When stressors represent a real or perceived threat to the neurobiological balance (homeostasis) of a person, physiological and behavioral responses are triggered in order to achieve adaptation and survival in the short run (i.e., allostasis). The protective and restorative allostatic processes of the body are mediated through the autonomic nervous system, the hypothalamic–pituitary–adrenal (HPA) axis, and the cardiovascular, metabolic and immune systems. However, over longer periods of time, the same response systems that are designed to protect and restore can be damaging and can cause or exacerbate symptoms, disease, and illness (i.e., allostatic load).

## THE EMOTIONAL MOTOR SYSTEM

The central stress response is mediated through the emotional motor system (EMS) of the central nervous system (CNS). The EMS refers to a network that includes the anterior cingulate cortex, hypothalamic nuclei, amygdala, periaqueductal gray, and brain stem nuclei (locus ceruleus, Barrington's nucleus, dorsal motor nucleus of the vagus, and rostral ventral medulla), which form the basis for vagal, parasympathetic, and sympathetic visceral efferent pathways. In Fig. 2, a simplified depiction of the four principal output functions of the EMS-mediated stress response, "ascending aminergic" refers to arousal, attentional, and emotional feeling output.

Although the terms "emotion" and "feeling" are commonly used interchangeably, they can be conceptualized as distinct dimensions of the stress response generated by the EMS, playing a critical role in maintenance of health and in cognitive processes, including perception, learning, and decision-making. Emotion is a collection of encoded stress responses triggered from parts of the brain to the body and to other parts of the brain via both neural and humoral routes, resulting in changes within the body and certain areas of the brain. Examples of emotion include fear, anger, disgust, and joy, each with unique physiological and behavioral expression. Feeling is the conscious emotional experience or mental state that commonly, but not necessarily, accompanies a given emotional stress response. For example, the physiologically expressed emotion of fear with associated gut symptoms of abdominal pain and diarrhea may or may not be accompanied by the emotional feeling of anxiety.

## THE MIND/BRAIN–GUT CONNECTION

The bidirectional neurobiological communication of the mind/brain–gut connection is critical to understanding the expression of the emotional stress response in the gut. The central stress response and allostasis can be triggered by both exteroceptive and interoceptive stressors. With an approximate external surface area of 2 square yards, the skin participates with the other senses in detection of exteroceptive stressors. The gut has an even larger internal surface area, 5250 square

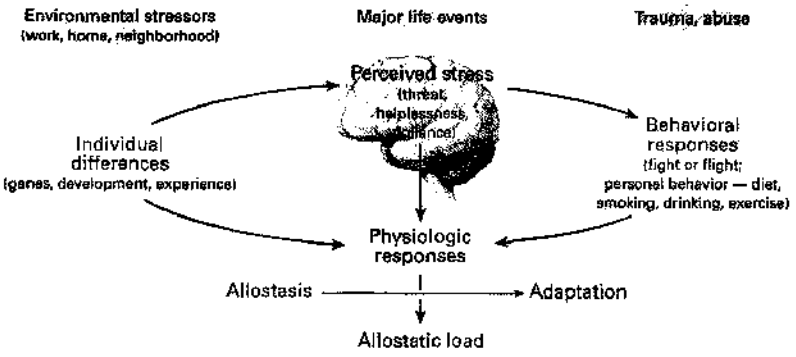


**FIGURE 1** The stress response and development of allostatic load. The perception of stress is influenced by experiences, genetics, and behavior. When the brain perceives an experience as stressful, physiologic and behavioral responses are initiated, leading to allostasis and adaptation. Over time, allostatic load can accumulate, and the overexposure to mediators of neural, endocrine, and immune stress can have adverse effects on various organ systems, leading to disease. Reprinted with permission from McEwen, B. S. (1998). Protective and Damaging Effects of Stress Mediators. *N. Engl. J. Med.* 338, 171–179. Copyright 1998, Massachusetts Medical Society, all rights reserved.

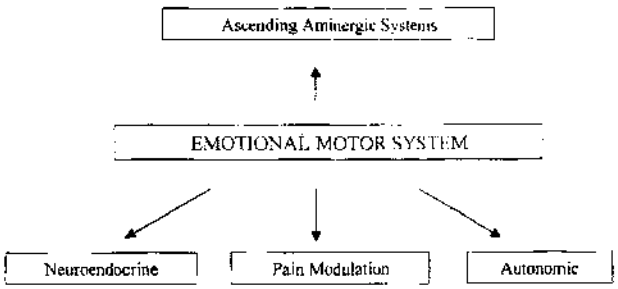


FIGURE 2 Major outputs of the emotional motor system. The emotional motor system refers to a set of parallel output pathways that are activated in response to perceived threat or fear. Alterations in these four pathways have been demonstrated in patients with irritable bowel syndrome. Reprinted from Mayer, E. A. (1999). Emerging Disease Model for Functional Gastrointestinal Disorders. *Am. J. Med.* 107(5A), 12S–19S. Copyright 1999, with permission from Excerpta Medica, Inc.

yards (the size of a football field), and detects visceral interoceptive stressors such as inflammation, infection, blood loss, and food intake.

The brain and gut both derive from the neural crest of the human embryo and share many of the same neurons and chemical transmitters, such as serotonin. The enteric nervous system (ENS) embedded in the wall of the gut and extending from the esophagus to the anus is one of three subdivisions of the autonomic nervous system (ANS), together with the sympathetic and parasympathetic divisions. Although bidirectionally linked and integrated with the CNS, the ENS is an enteric minibrain located close to the gut effector systems that it controls, i.e., the musculature, secretory glands, vasculature, and mucosal epithelium. Just as stereotypical emotional stress responses to threatening stressors are encoded within the EMS, the ENS stores a library of programs of defensive stress responses for different patterns of gut motor and secretory behavior that can either be activated by stressors interpreted by the brain or sensed locally within the gut. One example is the "power propulsion" (anal direction) response designed as a protective process to move digestive contents out of the digestive tract (symptoms include diarrhea and abdominal pain).

## GUT EMOTION AND FEELING

Joseph E. LeDoux and Emeran A. Mayer emphasized that stressor-triggered and encoded physiological emotional responses, such as fear and anger, are unique and usually generated unconsciously. For example, fear is associated with inhibition of upper gastrointestinal motility and secretion, which can result in symptoms of bloating, loss of appetite, nausea, and even vomiting. By contrast, anger is associated with stimulation of gastric contractions and acid secretion, which may be accompanied by symptoms of upper abdominal pain.

Visceral afferent information related to emotional gut responses modulates both emotional affective and cognitive mental function. Language expressions such as "my stomach is tied in knots" and "I hate your guts" imply common understanding of the linkage between emotional feelings, such as anxiety and anger, and specific and commonly unpleasant visceral gut experiences. Furthermore, the expression "it's my gut feeling" implies that visceral sensations relate to a prerational insight or "emotional intelligence," a term popularized by psychologist Daniel Goleman in his book of the same name.

## ROLE OF ALLOSTATIC LOAD IN DISEASE AND ILLNESS

Dysregulation of the central stress response system related to allostatic load contributes to the development of a variety of diseases and illnesses, including hypertension, atherosclerosis, central obesity, diabetes, the insulin resistance syndrome (metabolic syndrome x), and certain disorders of immune function. Chronically elevated corticosteroid levels induced by persisting stress may adversely affect hippocampal structure and function, which can result in deficits of both memory and cognition. Gastrointestinal diseases and illnesses adversely impacted by allostatic load include nonalcoholic fatty liver disease (also associated with the insulin resistance syndrome), gastroesophageal reflux disease (GERD), peptic ulcer disease, inflammatory bowel disease, and functional gastrointestinal disorders (FGID).

## FUNCTIONAL MEDICAL SYMPTOMS AND SYNDROMES

Functional illness is related to altered physiological function, absence of an identifiable structural or biochemical cause, and involvement of virtually any organ system with a variety of symptoms (most common symptoms are pain, discomfort, disturbed sleep, and loss of vitality). Such functional symptoms are also called "medically unexplained symptoms." Fibromyalgia (chronic and recurrent widespread aching pain and fatigue) is one example of a related functional syndrome that is a medically unexplained collection of symptoms. The most common FGID is irritable bowel syndrome (IBS), characterized by chronic and recurrent abdominal pain and/or discomfort associated with altered bowel function (constipation, diarrhea, or both).

Douglas A. Drossman pioneered the application to the pathophysiology of IBS a biopsychosocial model that

describes the interacting role of genetic, biological, psychosocial, and cognitive factors. Extending the perspective of this system, Emeran A. Mayer developed a disease model of FGID that is also based on Bruce S. McEwen's concepts of allostasis and allostatic load. An enhanced responsiveness of the central stress/emotion circuits to real or perceived exteroceptive or interoceptive stressors by IBS patients is reflected in altered modulation of gastrointestinal motility, secretion, permeability, and immune function, and altered perceptual and emotional response to visceral events.

## AFFECTIVE SYMPTOMS AND DISORDERS

The concepts of allostasis and allostatic load focus on the mind/brain as both the interpreter and responder and the target of real or perceived stressors/triggers. Emerging neurobiological models of the adverse consequences of allostatic load and the dysregulated central stress response help to explain the common association of emotional feelings and affective disorders, such as anxiety and depression, with the emotional gut symptoms of FGID, such as IBS. Furthermore, research confirms that depressive illness and hostility are both associated with cardiovascular and other systemic diseases. Similar therapeutic strategies may be applicable in the management of both affective disorders and functional disorders and certain diseases.

## MIND–BODY MEDICINE AND REDUCTION OF ALLOSTATIC LOAD

There is an emerging convergence of ancient, traditional, and modern scientific approaches to disease, illness, and healing. The neurobiological basis for mind–body, complementary and alternative medicine (CAM), and integrative medicine interventions is becoming increasingly understood. Mind–body medicine, which refers to the application of multidisciplinary methods based on the inseparable connection between the mind and the body and the complicated interactions that take place between thoughts, body, and the outside world, has the goal of restoring homeostasis and health by enhancing the natural healing capacities conferred by innate body systems.

Research has confirmed that stress reduction and certain mind- body cognitive behavioral interventions can significantly improve health outcomes and reduce the need for more expensive treatments in a variety of diseases and illnesses. Behavioral responses can be harmful or helpful (see Fig. 1). The objective is reduction of allostatic load (Fig. 3). Helpful strategies include

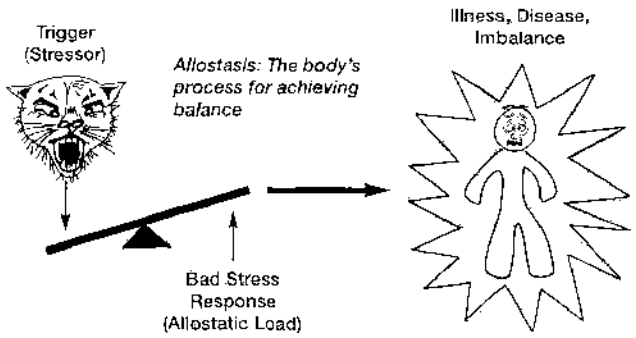


FIGURE 3 Disturbed homeostasis (imbalance). Reprinted with permission from Salt II, W. B. and Neimark, N. F. (2002). Irritable Bowel Syndrome and the MindBodySpirit Connection. Copyright 2002, Parkview Publishing, all rights reserved.

consistent commitment to healthy lifestyle choices (e.g., diet and exercise) and the development of effective coping styles that incorporate positive mental outlook and avoidance of both high-demand/low-control stressors and social isolation. Individuals can learn to activate mechanisms that oppose the stress response and induce what Harvard's Herbert Benson terms "the relaxation response" via various techniques (e.g., progressive relaxation, hypnosis, meditation, yoga, and breathing exercises).

### See Also the Following Articles

**Brain–Gut Axis • Enteric Nervous System • Irritable Bowel Syndrome • Neurogastroenterology • Psychosociology of Irritable Bowel Syndrome**

### Further Reading

Benson, H. (2002). Mind/Body Medical Institute web site (affiliated with Harvard Medical School and Beth Israel-Deaconess Medical Center). Retrieved at http://www.mbmi.org/.

Drossman, D. A. (1998). Presidential address: Gastrointestinal illness and the biopsychosocial model. *Psychosom. Med.* 60(3), 258–267.

LeDoux, J. E. (1996). "The Emotional Brain." Touchstone, New York.

Mayer, E. A. (1999). Emerging disease model for functional gastrointestinal disorders. *Am. J. Med.* 107(5A), 12S–19S.

Mayer, E. A., and Saper, C. B., eds. (2000). "The Biological Basis for Mind Body Interactions." Elsevier Science, San Diego.

McEwen, B. S. (1998). Protective and damaging effects of stress mediators. *N. Engl. J. Med.* 338, 171–179.

McEwen, B. S. (2002). "The End of Stress As We Know It." Joseph Henry Press, New York.

Salt, W. B. 2nd, and Neimark, N. F. (2002). "Irritable Bowel Syndrome and the MindBodySpirit Connection." Parkview Publishing, Columbus.

Van Uallie, T. B. (2002). Stress: A risk factor for serious illness. *Metabolism* 51(6, Suppl. 1), 40–45.

Wood, J. D. (2002). Neuropathophysiology of the irritable bowel syndrome. *J. Clin. Gastroenterol.* 35(1, Suppl.), S11–S22.

# Stress Ulceration

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**histamine-2 receptor antagonists** Pharmacologic agents that inhibit acid secretion by acting as specific antagonists of the histamine-2 receptor on the parietal cell.

**mucosal restitution** Early phase of gastrointestinal mucosal repair whereby damaged cells slough off and are replaced by viable cells.

**proton pump inhibitors** Substituted benzimidazoles that inhibit acid secretion by blocking the parietal cell $H^+$, $K^+$-ATPase.

**sucralfate** Basic aluminum salt of sucrose octasulfate; protects mucosal integrity locally without substantially altering gastric pH.

**Stress ulcer is a gastric mucosal injury typically seen in critically ill patients who require mechanical ventilation or have a coagulopathy. These ulcerations develop from a multifactorial process, with the primary insult being gastric ischemia. Patients in the intensive care unit can experience significant bleeding that is associated with increased mortality. Preventive strategies have focused on acid suppression and local mucosal protection.**

## RISK FACTORS

Patients admitted to the intensive care unit (ICU) are a heterogeneous group with variable risks for bleeding. The two strongest risk factors for stress ulcer bleeding are respiratory failure requiring mechanical ventilation for greater than 48 hours and coagulopathy (defined as platelet count of <50,000 cells/mm$^3$ or International Normalized Ratio of >1.5). Other risk factors include previous gastrointestinal bleeding, hypotension, trauma, burn injury (>35% of body surface), central nervous system injury, renal failure, hepatic failure, organ transplantation, and sepsis. However, many of these risk factors may simply represent surrogate markers for mechanical ventilation and/or coagulopathy.

## PATHOPHYSIOLOGY

Although incompletely understood, the pathophysiology of stress ulcer formation is the result of a multifactorial process. The proximal gastrointestinal tract maintains mucosal integrity with a microcirculation that provides nutrients and a route of elimination for toxins. Additionally, a mucus layer protects the gastric mucosa by forming a physical barrier to acid and other intraluminal irritants.

The major physiologic derangement in stress ulcer development is a loss of mucosal integrity. In the setting of severe physiologic stress, hypoperfusion leads to a cascade of events mediated by the overproduction of nitric oxide synthase. A reperfusion injury ensues in which increased production of oxygen free radicals, local intramural acidosis caused by back diffusion of luminal hydrogen ions, and a loss of washout effect combine to disrupt mucosal integrity.

In intracranial processes, hypergastrinemia may occur and lead to overproduction of acid. Other factors that may contribute to stress ulcer formation include reduced gastric epithelial cell restitution, abnormal gastric and small bowel motility, increased bile reflux, and nutritional disturbances.

## CLINICAL PRESENTATION

### Natural History

The majority of stress ulcerations are asymptomatic and clinically insignificant. In endoscopic studies, mucosal injury is found in greater than 75% of critically ill patients within 24 hours of admission. The typical mucosal injury seen is multiple, diffuse, superficial erosions in the gastric fundus and body; however, focal, deep ulceration can also be seen in both the stomach and the duodenum.

In clinical studies, the presentation of stress ulcer bleeding has been categorized as overt and clinically important bleeding. Overt bleeding is defined as hematemesis, gross blood or dark material resembling coffee grounds in nasogastric aspirate, hematochezia, or melena. Clinically important bleeding is defined as overt bleeding complicated by any one of the following events within 24 hours: (1) a spontaneous decrease in systolic blood pressure of > 20 mmHg, (2) an increase in heart rate of > 20 beats/min, (3) a decrease of > 10 mmHg of

 

systolic blood pressure shortly after sitting up, (4) a decrease in hemoglobin level of >2 g/dl, and (5) blood transfusion with no appropriate increase in hemoglobin level. In ICU patients, the estimated incidence of overt bleeding is 5% and the incidence of clinically important bleeding is 1–4%.

In a multicenter trial of critically ill patients, 31% of patients with one or two risk factors (mechanical ventilation and/or coagulopathy) had clinically important bleeding whereas only 0.1% of patients without these risk factors bled. Clinically important bleeding typically occurs within the first 2 weeks of ICU admission with a mortality of nearly 50%, a fivefold increase from those patients who did not experience bleeding.

### Diagnosis

The diagnosis of stress ulcer bleeding is confirmed by endoscopy when the typical findings of either erosions or ulcer are identified.

## THERAPY

If ulceration with high-risk stigmata (nonbleeding visible vessel or active bleeding) is found, endoscopic interventions such as injection of epinephrine and/or thermal therapy can lead to hemostasis with a reduced rebleeding rate. Concurrent medical therapy with intravenous proton pump inhibitor (PPI) is also indicated in patients with high-risk stigmata. Occasionally, angiography with embolization into the vessel that is the source of the bleeding or surgery is required to treat bleeding refractory to medical and endoscopic therapy.

## PREVENTION

Prophylaxis against stress ulcer in high-risk patients has become the standard of care in the ICU. Gastric pH-altering regimens such as antacids, histamine-2 receptor antagonists (H2RAs), and PPIs may prevent stress ulcer bleeding by maintaining intragastric pH >4, which inhibits pepsin and helps prevent clot dissolution.

### Antacids

Antacids control intragastric pH by buffering hydrogen ions. In a meta-analysis, antacids in comparison to placebo displayed a trend toward reducing both overt and bleeding and clinically important bleeding. No change in mortality was noted. In comparison to H2RAs, antacids displayed a trend toward greater bleeding. In comparison to sucralfate, antacids were somewhat more effective in preventing bleeding.

### H2RAs

In a meta-analysis, intravenous H2RAs (cimetidine or ranitidine), in comparison to placebo, significantly decreased both the rate of overt bleeding and clinically important bleeding. No change in mortality was noted. H2RAs displayed a trend toward decreased clinically important bleeding in comparison to both antacids and sucralfate. In a large, multicenter trial comparing ranitidine (50 mg intravenously every 6 hours) versus sucralfate (1 g intragastrically every 6 hours), clinically important bleeding was lower in patients receiving ranitidine in comparison to sucralfate (1.7 versus 3.8%, $p = 0.02$). During prolonged intravenous H2RA therapy, the development of tolerance may lead to a reduction in acid suppression.

### PPIs

Three small clinical trials have evaluated the use of omeprazole suspension delivered via nasogastric tube in mechanically ventilated patients. Two trials used omeprazole granules dissolved in sodium bicarbonate and one used intact omeprazole granules in water. In the study comparing omeprazole to ranitidine, the prevalence of clinically important bleeding was significantly less in the omeprazole group in comparison to ranitidine (6 versus 31%). All three studies had methodological limitations such as small sample size, open-label design, and variance in stress ulcer risk factors, prompting caution in the interpretation and application of the study results.

From a pharmacologic standpoint, intravenous PPIs suppress gastric acid to a greater extent than do intravenous H2RAs, and without the development of tolerance. Data are not yet available comparing intravenous PPIs to H2RAs in stress ulcer prophylaxis.

### Sucralfate

Sucralfate, the basic aluminum salt of sucrose octasulfate, protects mucosal integrity locally without substantially altering gastric pH. In a meta-analysis, sucralfate in comparison to placebo decreased overt bleeding significantly but did not reduce clinically important bleeding. Sucralfate was not superior to antacids or H2RAs in preventing overt or clinically important bleeding. Sucralfate was associated with a lower incidence of nosocomial pneumonia in comparison to antacids and H2RAs.

## Summary of Preventive Therapies

Based on the available data, stress ulcer prophylaxis is warranted only in high-risk critically ill patients such as those requiring mechanical ventilation or with significant coagulopathy, although it may be considered in patients with numerous other risk factors. Intravenous H2RAs are the preferred preventive strategy in these high-risk patients, with only 30 patients requiring therapy to prevent one episode of clinically significant bleeding, although PPIs may also prove effective in future trials.

## See Also the Following Articles

**Antacids • H2-Receptor Antagonists • Proton Pump Inhibitors • Stress**

## Further Reading

Beejay, U., and Wolfe, M. M. (2000). Acute gastrointestinal bleeding in the intensive care unit: The gastroenterologist's perspective. *Gastrointest. Clin. North Am.* 29(2), 309–336.

Cash, B. D. (2002). Evidence-based medicine as it applies to acid suppression in the hospitalized patient. *Crit. Care Med.* 30(Suppl.), S373–S378.

Cook, D. J., Fuller, H. D., Guyatt, G. H., *et al.* (1994). Risk factors for gastrointestinal bleeding in critically ill patients. *N. Engl. J. Med.* 330, 377–381.

Cook, D. J., Reeve, B. K., Guyatt, G. H., Heyland, D. K., Griffith, L. E., Buckingham, L., and Tryba, M. (1996). Stress ulcer prophylaxis in critically ill patients: Resolving discordant meta-analyses. *JAMA* 275, 308–314.

Fennerty, M. B. (2002). Pathophysiology of the upper gastrointestinal tract in the critically ill patient: Rationale for the therapeutic benefits of acid suppression. *Crit. Care Med.* 30(Suppl.), S351–S355.

Silen, W. (1987). Gastric mucosal defense and repair. *In* "Physiology of the Gastrointestinal Tract" (L. R. Johnson, ed.), pp. 1055–1069. Raven Press, New York.

Spechler, J. S. (2002). Peptic ulcer disease and its complications. *In* "Sleisenger and Fordtran's Gastrointestinal and Liver Disease" (M. Feldman, L. S. Friedman, and M. H. Sleisenger, eds.), 7th Ed., pp. 748–772. Saunders, Philadelphia.

Steinberg, K. P. (2002). Stress-related mucosal disease in the critically ill patient: Risk factors and strategies to prevent stress-related bleeding in the intensive care unit. *Crit. Care Med.* 30(Suppl.), S362–S364.

# Submucosal Tumors of the Gastrointestinal Tract

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**carcinoids** Indolent neuroendocrine tumors that originate in the mucosa but grow deep into the submucosa.

**duplication cysts** Congenital intestinal duplications that can be found in the walls of the esophagus, stomach, or duodenum.

**gastrointestinal stromal cell tumors** Rare mesenchymal neoplasms that can be found throughout the digestive tract.

**granular cell tumors** Generally benign growths that are derived from smooth muscle or Schwann cells.

**lipomas** Rare benign tumors of adipocytes that can occur throughout the gastrointestinal tract from the esophagus to the rectum.

**pancreatic rest** Ectopic pancreatic tissue located in the wall of the stomach or small intestine.

**submucosal tumor** A growth of tissue in the intestinal wall that originates from the submucosa, from the muscularis propria, or from extrinsic compression by adjacent structures.

**varices** Abnormally swollen or dilated blood vessels.

**Submucosal tumors (SMTs) are rare with a combined incidence estimated at 0.3% annually. However, SMTs are an increasingly common finding for general internists and gastroenterologists as more patients undergo diagnostic endoscopy or radiographic studies with oral contrast. Most SMTs are asymptomatic, and for some types, the natural history is not well understood. However, a few unique, sometimes subtle, characteristics can distinguish**

**them on radiographs and video endoscopy. Moreover, the emergence of endoscopic ultrasound (EUS) technology is allowing a better understanding of SMTs and is making evaluation of SMTs more accurate. By demonstrating the exact size and point of origin of a SMT, EUS helps to identify patients who may have a malignant lesion and may require surgery. For any given patient with a SMT, the ideal approach depends on its physical characteristics, its histology, and the clinical setting in which it was diagnosed. This article will describe how SMTs initially present and will summarize the distinguishing characteristics of the most common subtypes of SMTs. An approach to tissue diagnosis, treatment, and follow-up for each type of SMT will be emphasized.**

## IDENTIFICATION AND PRESENTATION

A submucosal tumor (SMT) is defined as a growth of tissue in the intestinal wall that originates from the submucosa, from the muscularis propria, or from extrinsic compression by adjacent structures (see Table I). Most SMTs are found incidentally on upper endoscopy where they appear as a mass or projection into the gastrointestinal lumen. Because they are covered by normal mucosa, some authors suggest that a better name for SMTs would be "subepithelial tumors."

In some cases, additional features can be seen on endoscopy. Stromal cell tumors, for example, frequently show two prominent lobes on video endoscopy. Lipomas are known to have a waxy hue and are very soft and "pillow-like" when explored with an endoscopic biopsy forceps.

SMTs may also be found by contrast radiography or computed tomography (CT) scan. When patients undergo barium radiography, a SMT will cause a well-demarcated filling defect with smooth borders; the lesion will displace the mucosal folds. CT scans can show the intramural mass of a SMT if the cuts are finer than the diameter of the mass. If a CT shows a homogeneous fat-tissue density structure in the wall of the colon, for example, the diagnosis of lipoma can be made with confidence.

**TABLE I Common Submucosal Lesions by Layer of Origin and Other EUS Features**

| Lesion | Borders | Echogenicity | Consistency |
|---|---|---|---|
| Submucosa | Smooth | | May be separated |
| Cyst | | Anechoic | May be separated |
| Lipoma | | Hyperechoic | Homogeneous |
| Carcinoid | | Hypoechoic | Heterogeneous |
| Varices | | Anechoic | |
| Muscularis propria | Smooth, irregular | Hypoechoic | Homogeneous |
| GIST | | | small lesions, homogeneous |
| | | | large lesions, may be heterogeneous |
| Extrinsic | Smooth | Isoechoic | Homogeneous |
| Spleen | | | |
| Liver | | | |

## EVALUATION

Although SMTs may be initially identified by endoscopy, radiographs, or CT scan, endoscopic ultrasound (EUS) provides a more complete description by delineating the originating wall layer in the gastrointestinal tract, identifying vascular invasion, and characterizing the internal milieu of the tumor.

A radial ultrasound transducer at the tip of an endoscope can demonstrate five layers of the gastrointestinal tract at 7.5 MHz: superficial mucosa, deep mucosa, submucosa, muscularis propria, and serosa. EUS can also image adjacent organs such as the pancreas, liver, gallbladder, spleen, kidneys, and adrenal glands. By definition, SMTs arise from the submucosa (third layer) or the muscularis propria (fourth layer) or are external to the gastrointestinal (GI) tract. The contents of the SMT will also create a characteristic echo pattern that is either bright (hyperechoic) or dark (hypoechoic) and either homogeneous or heterogeneous in consistency. The borders may be smooth or irregular on EUS. EUS can visualize SMTs sized from 5 to 60 mm. In a series of 15 resected specimens that were preoperatively evaluated by EUS, 87% were correctly sized by the technique. Some SMTs are more difficult to diagnose accurately by EUS. A study of interobserver agreement among nine expert endosonographers showed that most endoscopists agreed on the ultrasound diagnosis of cysts, lipomas, and extrinsic compressions, but for carcinoids, granular cell tumors, pancreatic rest tissue and metastases, the endoscopists tended to disagree.

## COMMON SUBMUCOSAL TUMORS

There are multiple types of submucosal tumors. They can be classified by the layer of origin in the gastrointestinal wall and further differentiated based on histology and natural history.

### Lesions in the Submucosa

#### *Lipoma*

Lipomas are rare benign tumors of adipocytes that can occur throughout the GI tract from the esophagus to the rectum. They are most often found in the colon.

Most do not cause symptoms; however, when they become larger than 1 cm, lipomas may cause abdominal pain, obstruction, bleeding, or dyspepsia.

On video endoscopy, lipomas appear spherical or round and may have a waxy hue rather than the pink of normal mucosa. When biopsy forceps are placed through the endoscope, lipomas show the "tenting" and "cushion" signs. Tenting refers to the mucosa being easily pulled off the lesion. With the cushion sign, pushing the forceps into the lesion causes a pillow-like depression in the lesion.

Superficial biopsies of lipomas will show only the normal overlying mucosa. Multiple biopsies in the same location or a biopsy that follows electrocautery through the mucosa can document the characteristic adipose tissue. Because lipomas contain a generous amount of fat, they may also be diagnosed by CT scan.

EUS images of lipomas show homogeneous, hyperechoic, and well-demarcated lesions that are fully contained in the submucosa (see Fig. 1). When the EUS images are pathognomonic, the diagnosis is secure and fine-needle aspiration (FNA) is not required. Follow-up endoscopy, however, may be considered at 2- to 4-year intervals to confirm that the lesion is not growing rapidly.

### *Carcinoid Tumor*

Carcinoids are indolent neuroendocrine tumors that originate in the mucosa but grow deep into the submucosa. The estimated incidence is 1 to 2 per 100,000 in the United States. They may produce a number of vasoactive substances and neurotransmitters, such as histamine, somatostatin, and catecholamines. An earlier embryologic classification scheme that organized carcinoids as foregut, midgut, or hindgut has given way to a system that emphasizes the organ involved and the presence of nuclear atypia, mitoses, and necrosis.

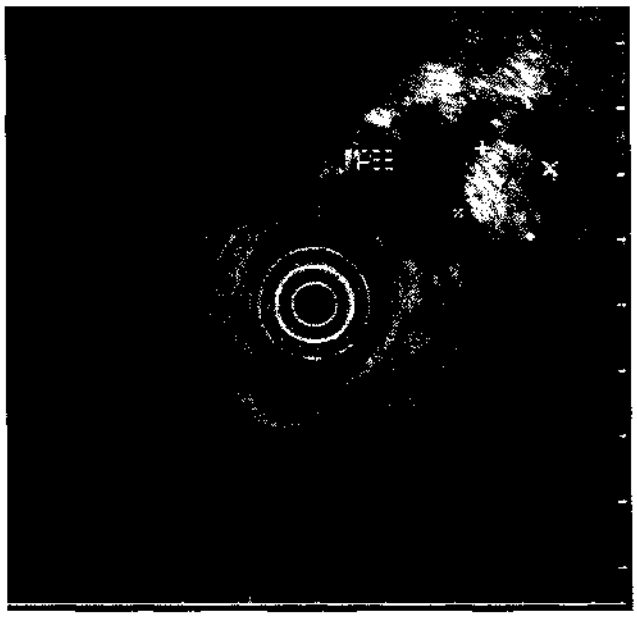

FIGURE 1 EUS image of duodenal lipoma showing hyperechoic lesion in submucosa with intact overlying superficial and deep mucosal layers.

In the United States, the appendix is the most common site for carcinoids. In this location, tumors are usually found incidentally at the time of appendectomy as they rarely produce symptoms. Carcinoids in the small bowel, appendix, and right colon may metastasize to the liver. When these metastases severely injure the liver, patients may experience the constellation of flushing, asthma, and diarrhea that is characteristic of carcinoid syndrome. In a large database review, tumors in the distal two-thirds of the colon rarely produced systemic symptoms but were most likely to present with bleeding. Gastric carcinoids are often multicentric and arise in settings of hypergastrinemia such as Zollinger-Ellison syndrome or atrophic gastritis. Gastric carcinoids also occur sporadically. In the stomach, carcinoids may cause flushing without the other elements of the carcinoid syndrome.

When viewed endoscopically, carcinoids usually appear as a smooth, yellowish mass sometimes with an umbilicated ulceration. Histologic diagnosis can be made with mucosal biopsy. EUS can be used to evaluate the critical features of size, depth of invasion, and lymph node metastases. Typically, carcinoids appear hypoechoic and homogeneous and are located in the submucosa.

Tumors with dimensions greater than 2 cm or penetration of the muscularis propria are associated with increased metastatic risk. Treatment requires surgical excision. For tumors in the colon and small bowel, the resection must include wide margins with regional lymph node dissection. Appendiceal carcinoids that are less than 2 cm can be managed more conservatively. Because these small appendiceal tumors are unlikely to recur locally after resection, local excision is sufficient. For lesions greater than 2 cm, one-third of patients will have nodal or regional metastases at the time of diagnosis and right hemicolectomy should be considered.

Small gastric carcinoids that arise in the setting of pernicious anemia and chronic atrophic gastritis are generally indolent lesions. As fewer than 10% metastasize, these carcinoids may also be managed with local excision. Endoscopic removal of gastric carcinoids is becoming more common. If the excision is complete based on follow-up video endoscopy and EUS, then

periodic endoscopic surveillance is recommended at 1- to 2-year intervals.

A 30-year review of individuals diagnosed with carcinoid tumors at one center showed that patient outcome is influenced by age, stage at diagnosis, and urinary level of 5-hydroxyindoleacetic acid. Because many pancreatic and small bowel carcinoids are metastatic at the time of diagnosis, they tend to have the worst overall outcomes with a 5-year survival of approximately 50% compared to 80–85% for appendiceal and rectal carcinoids.

### Pancreatic Rest

Pancreatic rest is ectopic pancreatic tissue located in the wall of the stomach or small intestine. Pancreatic rests are thought to develop early in embryogenesis before the fusion of the dorsal and ventral pancreatic anlage tissue. The estimated prevalence at autopsy is 1–2% but they are seen in fewer than 1 in 1000 endoscopies. Most gastric lesions are seen within 6 cm of the pylorus. The typical endoscopic image of an umbilicated nodule is nonspecific. EUS shows a heterogeneous hyperechoic lesion in the submucosa. An echo-free ductal region in the basal aspect of the lesion is characteristic of ectopic pancreas. Generally, pancreatic rests are asymptomatic but there are rare reports of obstruction, pancreatitis, and development of pancreatic neoplasm.

### Varices

Collateral vessels in the stomach, esophagus, small bowel, and colon form as a consequence of portal hypertension. They are seen in approximately 60% of decompensated cirrhotics and 30% of compensated cirrhotics at the time of presentation. Endoscopically, varices present as protuberant columns in the esophagus and are easy to diagnose visually. In the stomach, however, gastric varices may be mistaken for prominent folds in the gastric fundus. EUS can be helpful by providing characteristic images of echo-free intramural and extramural vessels with visible blood flow. Varices may be seen in the mucosa, submucosa, or muscle layer or may be para-esophageal or para-gastric.

### Duplication Cyst

Duplication cysts are congenital intestinal duplications that can be found in the walls of the esophagus, stomach, or duodenum. Because they do not communicate with the lumen and can contain actively secreting glands, they can enlarge and produce symptoms or become complex cystic masses as secretions build up. In general, they are asymptomatic and benign. EUS demonstrates a smooth-bordered, submucosal lesion that is anechoic. EUS-guided FNA of duplication cysts is usually not recommended out of concern for introducing infection.

### Granular Cell Tumor

Granular cell tumors are generally benign growths that are derived from smooth muscle or Schwann cells. Only 1% involve the gastrointestinal tract, in which case they are found most commonly in the esophagus. They may also be found in the anal canal, where they can be confused with hemorrhoids. They appear as polypoid growths on endoscopy and require deep mucosal biopsy for diagnosis. EUS images usually show a hypoechoic mass that occupies the deep mucosal layer or submucosa. Histologically, they consist of masses of cells that appear like histiocytes with a granular, eosinophilic cytoplasm. Although the probability of malignant transformation is low, endoscopic or surgical resection is advisable especially if serial examinations demonstrate interval changes in size or invasiveness. Metastatases appear rarely. Although researchers have reported a case of multiple esophageal and gastric granular cell tumors with nuclear features of malignancy, the patient was cured by local resection.

### Muscularis Propria Lesions

#### *Stromal Cell Tumor*

Gastrointestinal stromal cell tumors (GISTs) are rare mesenchymal neoplasms that can be found throughout the digestive tract (Fig. 2). The vast majority (90%) originate in the stomach and small intestine and 10–30% may be malignant with intra-abdominal metastases. Formerly classified as leiomyomas and leiomyosarcomas, GIST is the new unifying nomenclature for all gastrointestinal mesenchymal tumors with unique genetic and histochemical features. GIST describes most of what were formerly considered leiomyomas and leiomyosarcomas.

GISTs are thought to arise from a stem cell with multipotent differentiation. Many GISTs show differentiation toward the pacemaker cells of the gastrointestinal tract, the interstitial cells of Cajal. Others exhibit features seen in smooth muscle and neural tissues. Histologically, GISTs show spindle cells growing in fasicles or sheets of epithelioid-type cells. GISTs are highly vascular and frequently present with gastrointestinal hemorrhage.

On EUS, stromal cell tumors are hypoechoic and arise from the muscularis propria or muscularis

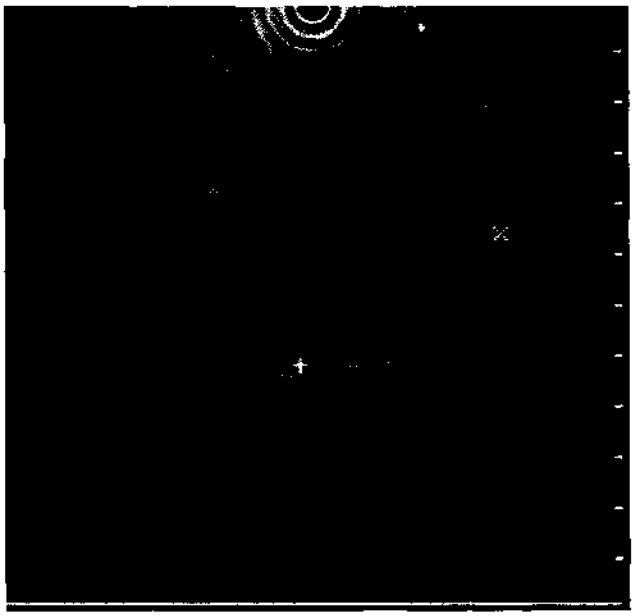

**FIGURE 2** EUS image of GIST in gastric wall showing heterogeneous, hypoechoic lesion involving muscularis propria.

mucosa. The most reliable method for determining malignancy of a GIST is immunohistochemical and genetic analysis of the specimen by surgical pathology. GISTs are classified as having low, high, or indeterminate malignant potential based on the presence of several criteria that can be determined by EUS and surgical pathology. Size greater than 3 cm, a high mitotic count per high-powered field (HPF), the presence of tumor necrosis, nuclear pleomorphism, dense cellularity, an alveolar or clustered cell pattern, and microscopic invasion of the lamina propria or blood vessels are predictors of high malignant potential (Table II). Finding any two of these features suggests that a stromal tumor has high malignant potential. A stromal tumor with only one of these traits is considered a tumor with uncertain malignant potential. If these criteria are absent, the tumor is benign. Histopathology is the gold standard for determining malignant potential. As a part of this process, the results of 50 HPFs are tabulated. FNA cytology provides insufficient material to definitively determine malignant potential.

**TABLE II Submucosal Tumors: Predictors of Malignancy**

| EUS | Histologic |
|---|---|
| Irregular margins | >50 mitoses per HPF |
| Size >3 cm | Tumor necrosis |
| | Nuclear pleomorphism |
| | Dense cellularity |
| | Alveolar or clustered cell pattern |
| | Microscopic invasion of the lamina propria or blood vessels |
| Cystic spaces | Missense mutation of c-kit gene |
| Lymphadenopathy | |

The missense mutation of the c-kit gene, which codes for a growth factor receptor with tyrosine kinase activity, has recently been identified as a molecular biologic marker for increased recurrence of GISTs and higher mortality. Assays for c-kit and CD34 performed on fine-needle aspirates may improve the diagnostic yield of FNA in settings where malignant GIST is suspected. Research is also ongoing to delineate the sensitivity of EUS criteria alone in the evaluation of stromal tumors. In one series of 56 GISTs studied by EUS, the presence of two out of three characteristics—irregular extralumenal margins, cystic spaces, and malignant-appearing lymphadenopathy—had a positive predictive value of 100% for malignant or borderline malignant histology. Other researchers studied the Doppler characteristic of GISTs and reported that turbulent, pulsatile flow was highly sensitive for malignancy (100%).

True leiomyomas are now thought to be rare in the GI tract, occurring most often in the esophagus or gastric cardia. They are composed of spindle cells but are less cellular than GISTs and immunohistochemically they differ by not expressing CD34 or CD117 (c-kit).

Suspected stromal cell tumors that are symptomatic and associated with bleeding, obstruction, or pain should be removed. Additionally, GISTs that are greater than 3 cm or increasing in size when seen in follow-up should be removed surgically to prevent metastatases. Laparoscopic resection of GISTs has been described. Although metastatic GISTs are generally highly resistant to chemotherapy, the new tyrosine kinase inhibitor STI571 has been reported to be highly active against GIST in a patient with metastatic disease.

## Extrinsic Compression

A number of adjacent structures can produce extrinsic compression on the gastrointestinal tract and appear as submucosal lesions on video endoscopy. Adjacent organs such as the spleen as well as lymph nodes, and pancreatic pseudocysts should be considered in the differential. EUS can be helpful in these situations. If a lesion is extralumenal, shows no relationship with layers of the gastrointestinal tract, and moves independently of the mucosa with the patient's respirations, then the mass is most likely external to the gastrointestinal tract.

TABLE III Submucosal Tumors: Indications for Resection

| |
|---|
| Size >3 cm |
| Symptoms: pain, bleeding, or obstruction |
| Interval enlargement |
| Cystic spaces |
| Lymphadenopathy |

## BIOPSY AND REMOVAL

Following characterization of an SMT by EUS, consideration should be given to periodic surveillance, biopsy, or excision. There are several methods for biopsy of SMTs. Utilizing the deep-well biopsy technique is one option whereby repeated pinch biopsies of the same point denude the mucosa and yield submucosal tissue. Alternatively, the top layer of mucosa can be removed by snare electrocautery and the submucosa can then be sampled. EUS and FNA of submucosal tumors can help determine tissue type but may not be able to demonstrate malignancy.

Most authors recommend surgical or endoscopic excision if lesions are greater than 3 cm in diameter or if they are producing symptoms (see Table III). An SMT that is shown by EUS to arise from the deep mucosa can be removed safely by conventional endoscopic polypectomy techniques. Saline injection may facilitate snare polypectomy.

In one case series, researchers used EUS to identify the wall layer of origin and to exclude characteristics suspicious for malignancy in 54 SMTs. Endoscopic resection was then performed for all masses arising in submucosa or muscularis mucosa. Muscularis propria lesions underwent mucosectomy followed by deep biopsy. Two of the 54 patients had biopsies showing malignancy. Although this procedure was safe and led to no perforations, the results suggest that EUS criteria alone may not identify all malignant lesions that require surgical removal.

## CONCLUSION

In conclusion, gastroenterologists and internists may consider the endoscopic and EUS characteristics of SMTs in order to make a presumptive diagnosis of the lesion's histology and predict its behavior. With this information, a strategy for surgical or endoscopic removal or surveillance can be planned. All lesions with features that suggest malignancy should be removed. Additionally, any SMT that is large, increasing in size, or associated with symptoms should be considered for removal. Fortunately, most SMTs are benign. As imaging and histopathologic techniques improve, there may be enhanced, noninvasive approaches for the diagnosis and treatment of SMTs.

## See Also the Following Articles

**Barium Radiography • Computed Tomography (CT) • Endoscopic Ultrasonography**

## Further Reading


Axelrad, A. M., and Fleischer, D. E. (1998). Esophageal tumors. *In* "Gastrointestinal and Liver Disease" (M. Feldman, M. H. Sleisenger, and B. F. Scharschmidt, eds.), Vol. 1, pp. 540–554. W. B. Saunders, Philadelphia, PA.

Chung, S., and Roberts-Thomson, I. C. (2001). Gastrointestinal: Pancreatic rests. *J. Gastroenterol. Hepatol.* 14, 829.

Dagher, L., and Burroughs, A. (2001). Variceal bleeding and portal hypertensive gastropathy. *Eur. J. Gastroenterol. Hepatol.* 13, 81–88.

Ernst, S. I., Hubbs, A. E., Przygodzki, R. M., Emory, T. S., Sobin, L. H., and O'Leary, T. J. (1998). KIT mutation portends poor prognosis in gastrointestinal stromal/smooth muscle tumors. *Lab. Invest.* 78, 1633–1636.

Goldschmiedt, M., and Gutta, K. (1998). Other tumors and diseases of the pancreas. *In* "Gastrointestinal and Liver Disease" (M. Feldman, M. H. Sleisenger, and B. F. Scharschmidt, eds.), Vol. 1, pp. 895–901. W. B. Saunders, Philadelphia, PA.

Gress, F., Schmitt, C., Savides, T., *et al.* (2001). Interobserver agreement for EUS in the evaluation and diagnosis of submucosal masses. *Gastrointest. Endosc.* 53, 71–76.

Iwase, H., Kusugami, K., Suga, S., and Kyokane, K. (1997). Color Doppler-enhanced endoscopic ultrasonographic diagnosis of upper gastrointestinal submucosal lesions. *Dig. Endosc.* 9, 116–121.

Joensuu, H., Roberts, P. J., Sarlomo-Rikala, M., *et al.* (2001). Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. *N. Engl. J. Med.* 344, 1052–1056.

Kawamoto, K., Yamada, Y., Utsunomiya, T., *et al.* (1997). Gastrointestinal submucosal tumors: Evaluation with endoscopic US. *Radiology* 205, 733–740.

Kindblom, L. G., Remotti, H. E., Aldenborg, F., and Meis-Kindblom, J. M. (1998). Gastrointestinal pacemaker cell tumor (GIPACT): Gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. *Am. J. Pathol.* 152, 1259–1269.

Kojima, T., Takahashi, H., Parra-Blanco, A., Kohsen, K., and Fujita, R. (1999). Diagnosis of submucosal tumor of the upper GI tract by endoscopic resection. *Gastrointest. Endosc.* 50, 516–522.

Kulke, M. H., and Mayer, R. J. (1999). Carcinoid tumors. *N. Engl. J. Med.* 340, 858–868.

Lasota, J., Jasinski, M., Sarlomo-Rikala, M., and Miettinen, M. (1999). Mutations in exon 11 of c-Kit occur preferentially in malignant versus benign gastrointestinal stromal tumors and do not occur in leiomyomas or leiomyosarcomas. *Am. J. Pathol.* 154, 53–60.

Lewin, K. J. (1992). Mesenchymal tumors. *In* "Gastrointestinal Pathology and Its Clinical Implications" (K. J. Lewin, R. H. Riddell, and W. M. Weinstein, eds.), Vol. 1, pp. 284–341. Igaku-Shoin, New York.

Li, S. Q., O'Leary, T. J., Buchner, S. B., *et al.* (2001). Fine needle aspiration of gastrointestinal stromal tumors. *Acta Cytol.* 45, 9–17.

Miettinen, M., Sarlomo-Rikala, M., and Lasota, J. (1999). Gastrointestinal stromal tumors: Recent advances in understanding of their biology. *Hum. Pathol.* 30, 1213–1220.

Modlin, I. M., and Sandor, A. (1997). An analysis of 8305 cases of carcinoid tumors. *Cancer* 79, 813–829.

Onaitis, M. W., Kirshbom, P. M., Hayward, T. Z., *et al.* (2000). Gastrointestinal carcinoids: Characterization by site of origin and hormone production. *Ann. Surg.* 232, 549–556.

Palazzo, L., Landi, B., Cellier, C., Cuillerier, E., Roseau, G., and Barbier, J. P. (2000). Endosonographic features predictive of benign and malignant gastrointestinal stromal cell tumours. *Gut* 46, 88–92.

Roesch, T., Kapfer, B., Will, U., *et al.* (1999). Endoscopy alone is not sufficient for a reliable diagnosis of upper GI submucosal tumors (SMT). *Gastrointest. Endosc.* 49, AB211.

Rosch, T., Lorenz, R., Dancygier, H., von Wickert, A., and Classen, M. (1992). Endosonographic diagnosis of submucosal upper gastrointestinal tract tumors. *Scand. J. Gastroenterol.* 27, 1–8.

Seidal, T., and Edvardsson, H. (2000). Diagnosis of gastrointestinal stromal tumor by fine-needle aspiration biopsy: A cytological and immunocytochemical study. *Diagn. Cytopathol.* 23, 397–401.

Wolfsohn, D. M., Savides, T. J., Easter, D. W., and Lyche, K. D. (1997). Laparoscopy-assisted endoscopic removal of a stromal-cell tumor of the stomach. *Endoscopy* 29, 679–682.

Yasuda, K. (2000). Gastrointestinal lesions. *In* "The Handbook of Endoscopic Ultrasonography in Digestive Tract," Vol. I, pp. 45–82. Blackwell Science, Malden, MA.

# Substance P

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**capsaicin** Natural ingredient of hot peppers of the genus *Capsicum*, the pungent ingredient of many "hot" and spicy foods. A subtype of primary afferent neurons is sensitive to capsaicin; at low doses, capsaicin stimulates these neurons and is toxic to the neurons at high doses or after prolonged treatment.

**chemical coding** Particular combination of neurotransmitters, neuropeptides, and other neuronal chemical markers characteristic of a particular class of neuron.

**dorsal root ganglia** Series of paired neural ganglia adjacent to the spinal cord; contain the neuronal cell bodies of capsaicin-sensitive primary afferent nerves as well as other afferent nerves.

**enteric nervous system** Neurons and supporting cells found within the walls of the gastrointestinal tract, including the pancreas and gallbladder.

**myenteric plexus (Auerbach's plexus)** Network of nerves and small ganglia that lie in the plane between the external longitudinal and inner circular layers of smooth muscle in the muscularis externa of the intestine.

**submucous plexus (Meissner's plexus)** Network of small ganglia and nerves located in the submucosa of the intestine.

**tachykinins** Family of neuropeptides sharing the same carboxyl-terminal amino acid sequence comprising the molecular center of biological activity of each peptide (F-x-G-L-M-amide). The mammalian tachykinins include substance P, neurokinin A, neuropeptide K, neuropeptide γ, and neuropeptide B.

**Substance P, a peptide composed of 11 amino acids, is expressed by neurons in the central, peripheral, and enteric nervous systems. Substance P is a major neurotransmitter in the gastrointestinal tract; it affects motility, secretion, and inflammation and can cause vomiting by an action in the central nervous system. Most actions of substance P are mediated by the neurokinin-1 receptor, thus excellent receptor antagonists have been developed to aid in differentiation of physiological versus pharmacological actions of substance P. These receptor antagonists may also prove to be of therapeutic value in treating substance P-associated inflammatory bowel disease, acute intestinal inflammation, and chemotherapy-induced nausea and vomiting.**

## INTRODUCTION

The 11 amino acids of the peptide substance P (SP) are arranged in the sequence RPKPQQFFGLM-amide.

Substance P is a member of the tachykinin family of mammalian neuropeptides. Other mammalian tachykinins include neurokinin A (NKA), the NKA-related peptides neuropeptide K (NPK) and neuropeptide γ (NPγ), and neurokinin B (NKB). Substance P got its unusual name from its discoverers, who identified an intestine-contracting activity extracted from equine intestine (it was then called preparation P). The tachykinins are named for their rapid ability to act on gut tissues, compared to the slower acting bradykinins. Substance P is encoded by the preprotachykinin I (PPT I) gene. Four mRNAs, termed α-PPT I, β-PPT I, γ-PPT I, and δ-PPT I, can be generated from the gene for PPT I by alternative mRNA splicing. The α-PPT I and δ-PPT I mRNAs encode only SP whereas the β-PPT I and γ-PPT I mRNAs encode both SP and NKA. Precursor proteins are synthesized from all four mRNAs and subsequent posttranslational processing generates the tachykinin peptides. β-PPT I and γ-PPT I proteins are subject to multiple proteolytic cleavages, resulting in the generation of NPK and NPγ, respectively, as well as SP and NKA. NKB is encoded by the PPT II gene, which does not encode any other tachykinins. Thus, although the genome contains only one gene for SP, the mRNA transcribed from the gene and the precursor proteins translated from the mRNAs can be processed in multiple ways to result in the expression of various combinations of SP, NKA, NPK, and NPγ in nerves.

In the gastrointestinal tract of the rat, the only species in which PPT I has been examined in detail, γ-PPT I mRNA comprises 80–90% of the total tachykinin RNA and β-PPT I mRNA and α-PPT I mRNA account for 10–20% and less than 1%, respectively. Thus, all members of the tachykinin family of neuropeptides except NKB are probably expressed in the gut. Three receptors correspond to the three major mammalian tachykinins. All three tachykinin receptors are G-protein-coupled receptors. Each receptor exhibits its highest affinity binding to a different tachykinin: SP has highest affinity for the neurokinin-1 (NK-1) receptor, NKA has highest affinity for the neurokinin-2 (NK-2) receptor, and NKB has highest affinity for the neurokinin-3 (NK-3) receptor. However, all three receptors can interact with all three mammalian tachykinins pharmacologically and it is possible that they do so physiologically as well. Substance P has been shown to stimulate several second-messenger systems coupled to the NK-1 receptor, i.e., inositol 1,4,5-trisphosphate, calcium, cyclic adenosine monophosphate (cAMP), mitogen-activated protein (MAP) kinase, and arachidonic acid.

Substance P was originally discovered in extracts of gastrointestinal tissue and was shown to contract gastrointestinal muscle in 1931. Studies of the role of SP in regulating the gastrointestinal tract have continued unabated since the 1930s and are still contributing insights into the nature of SP. Because of its potential importance in understanding the mechanisms of normal physiology and serving as the basis for potential new therapies for various diseases, SP is one of the best studied neuropeptides. In addition to detailed knowledge of the molecular biology of the peptide and its receptor, great strides have been made in understanding the pharmacology of SP, including the development of multiple selective agonists and antagonists for the NK-1 receptor. In the gut, SP is an important neurotransmitter both in enteric neurons (those intrinsic to the gut) and in extrinsic primary afferent nerves (the cell bodies of which are located adjacent to the spinal cord in the dorsal root ganglia). Various specific stimuli cause the release of SP and it has a predominantly excitatory action on gut nerve, muscle, and glands.

## GASTROINTESTINAL MOTILITY

The muscle layers of the gut (muscularis externa and muscularis mucosae) are innervated by a dense array of SP-containing nerve fibers, most of which originate from the enteric nervous system. The neuronal cell bodies in the enteric nervous system are in the myenteric plexus (MP), located between the inner circular and the outer longitudinal layers of smooth muscle of the muscularis externa, and the submucosal plexus (SMP), located in the submucosa. The SP-expressing enteric neurons have been mapped in detail in the guinea pig intestine such that their projections within and between the nerve plexuses and to the muscle layers and mucosa are well established. Although the neuroanatomy of gastrointestinal SP is not as well known in species other than the guinea pig, there do not appear to be major functional differences among mammalian species. The physiological functions of neurons depend on their chemical coding (the combination of neurotransmitters, neuropeptides, and other neuronal chemical markers characteristic of a particular neuron) and morphological characteristics, and studies of these features of enteric SP neurons have revealed roles as sensory neurons, interneurons, and motor neurons. Almost all MP and SMP SP neurons in the guinea pig intestine coexpress acetylcholine (ACh) whereas the extrinsic SP-expressing neurons coexpress calcitonin gene-related peptide (CGRP) and are sensitive to capsaicin, the pungent ingredient of hot peppers. Enteric SP neurons are not sensitive to capsaicin. Thus, it is possible to determine the intrinsic versus extrinsic source of SP in the gut by administering capsaicin, which acts as

an excitotoxin by first selectively stimulating and then, at higher doses or longer times, defunctionalizing extrinsic primary afferent, but not intrinsic, enteric neurons.

Various stimuli, including electrical depolarization, distension of the gut wall, intraluminal acid in the stomach, inflammation, various neurotransmitters and hormones, and capsaicin, can elicit SP release in the gut. Tachykinins enhance motor activity in virtually all regions and layers of the mammalian gut. Sometimes this action is a direct one on muscle, but in other cases, it reflects activation of enteric neurons that stimulate the muscle by release of ACh. A further complication arises when it is remembered that nerves that express the PPT I gene products most often corelease NKA and/or the NKA-like peptides NPK or NPγ along with SP. Furthermore, NK-1 receptors are expressed by both nerves and muscle cells whereas NK-2 receptors are mostly limited to smooth muscle cells. As a final complication, even though most tachykinin actions on gut motility are stimulatory, they can also inhibit gut muscle by stimulating inhibitory neural pathways or by interrupting stimulatory pathways. Most of the stimulatory actions of SP and NKA on gastrointestinal motility, especially in the case of peristalsis, are in synergism with ACh, with which they are coreleased from enteric neurons.

In studies of the human esophagus *in vitro*, tachykinins stimulate contraction of the lower esophageal sphincter (LES) and esophageal body via NK-2 receptors. In animal studies, tachykinins facilitate swallowing of fluids and increase LES pressure. In some species, SP causes only a transient LES contraction that is followed by a prolonged relaxation mediated by NK-1 receptors. It is not known if SP plays a major physiological role in normal human esophageal function.

Most of the information available about the effects of SP on gastric motility comes from animal studies. In the rat, injection of SP can either stimulate or inhibit gastric emptying and transit of a liquid meal, depending on whether parasympathetic or sympathetic reflexes are simultaneously activated. In the cat and dog, systemic administration of SP induces phasic contraction of the stomach via ACh release. Overall, SP is primarily stimulatory to gastric motility.

In the human small intestine and colon, NK-1 receptors are expressed by smooth muscle cells in the muscularis externa and muscularis mucosae and on neurons in the MP, and NK-2 receptors are expressed by smooth muscle but not by enteric neurons. This distribution correlates well with the observations that NKA directly stimulates human intestinal muscle contraction and that the effects of SP seem to occur indirectly via nerves. Intestinal peristalsis is a form of integrated propulsive motility resulting from the sequential activation of ascending excitatory and descending inhibitory reflexes initiated by local stretch of the intestinal wall, and resulting in propulsion of the contents of the intestine aborally. Because local stretch of the intestinal wall is the major stimulus for peristalsis, the role of tachykinins in the ascending contraction and descending relaxation of intestinal circular muscle in response to stretch or radial distension of the gut wall has been examined in detail. The peristaltic reflex is complex, consisting of distension-sensitive enteric sensory nerves, interneurons, orally projecting excitatory motor neurons to cause ascending contraction, and aborally projecting inhibitory motor neurons to cause descending relaxation. A variety of experimental approaches, including the administration of tachykinin receptor antagonists, SP desensitization, and SP immunoneutralization, have been used to demonstrate that SP and ACh are involved in the ascending reflex contraction caused by gut wall distension and that the descending relaxation is independent of tachykinins.

Additional analyses with antagonists selective for the NK-1 or NK-2 receptors have revealed that NK-2 receptors primarily mediate ascending reflex contraction in the guinea pig intestine, although some involvement of NK-1 receptors is also evident. It has also been demonstrated that stretch-induced ascending contraction, but not descending relaxation, of the human jejunum and rat colon is associated with release of endogenous SP and NKA. The concept that tachykinins are involved in the regulation of gastrointestinal propulsive motility *in vivo* is supported by the inhibition of gastric emptying and gastrointestinal transit in rats after administration of a tachykinin receptor antagonist.

Substance P contracts the human gallbladder by a direct effect on smooth muscle cells, but the physiological significance of this effect is not known.

## GASTROINTESTINAL SECRETION

There is a large body of evidence that SP participates, along with several other sialogogic messengers, in the parasympathetic regulation of salivary secretion. In rats, release of SP (and NKA) from the parotid glands is increased after nerve stimulation. In addition, the tissue content of SP is greatly reduced after prolonged stimulation of the parasympathetic but not sympathetic nerves supplying the salivary glands. Salivation, which also decreases after prolonged nerve stimulation, is restored by infusion of subthreshold doses of SP.

Tachykinin receptor antagonists reduce salivary output to parasympathetic nerve stimulation in the rat. The salivation evoked by sympathetic nerve stimulation in the rat is not affected by tachykinin receptor antagonists. The stimulatory effect of SP on salivation in rats and other species is potentiated by the coreleased neuropeptide vasoactive intestinal polypeptide (VIP). It is likely that SP is a physiologically important regulator of salivation in animals and people.

In contrast, the weak and variable effects of SP on gastric secretion suggest that the peptide does not play a major role in regulating gastric secretion. The currently available evidence supports only a potential modulatory influence of SP on the secretory functions of the stomach. In addition, there appear to be major species differences in the effects of SP on gastric secretion. For example, SP does not affect basal gastric acid secretion in rats or dogs but SP does stimulate gastric acid secretion in cats. Similar differences have been noted in the effects of SP on stimulated gastric acid secretion. The actions of SP on gastric acid secretion are so divergent that the only conclusion possible is that its effects depend on the species studied, the experimental conditions used, and the particular stimulus used to stimulate secretion. A good way to test the hypothesis that SP plays a physiological role in regulating gastric acid secretion would be to test the effects of NK-1 receptor antagonists, but this does not appear to have been done yet. Based on the evidence that SP is a potent pepsigogue in dogs and guinea pigs, it is possible that SP is a physiologically significant regulator of pepsinogen secretion. Pepsinogen is the inactive precursor of the proteolytic enzyme, pepsin, in the stomach. Pepsinogen is secreted by gastric chief cells, which have been shown to express NK-1 receptors, and is converted to pepsin in the gastric lumen by gastric acid.

There is strong evidence that SP is an important stimulant of secretion in the small intestine and colon. Systemic administration of SP induces a net secretion of water, sodium, potassium, and chloride into the small intestine of dogs, cats, and ferrets. SP stimulates an enteric neural reflex that results in the activation of secretomotor VIP neurons. A component of the SP effect can also be accounted for by a direct effect of SP on the mucosal epithelium. SP stimulates secretion by increasing the short circuit current ($I_{sc}$), an index of electrogenic anion secretion. The increased $I_{sc}$ is accompanied by a net secretion of sodium, chloride, and bicarbonate. The relative degree to which the SP effect is mediated by nerves versus direct effects on the mucosal epithelium varies with the type of tachykinin agonist used and the region of intestine studied. In the porcine and guinea pig small intestines, both the neural and epithelial responses are mediated by NK-1 receptors. The situation may be different in other species. However, the involvement of NK-1 receptors is consistent with the observation that secretomotor neurons in both the MP and SMP express NK-1 receptors. The stimulant action of SP on $I_{sc}$ in the small intestine requires calcium influx into the tissue because it is inhibited by removal of extracellular calcium or by pretreatment with verapamil, a calcium channel-blocking drug. The sodium/potassium/chloride cotransport mechanism has also been demonstrated to be important in SP-evoked stimulation of $I_{sc}$.

In the rat colon, SP converts fluid absorption into net fluid secretion. The secretory responses to NK-1 and NK-2 receptor agonists are suppressed by tetrodotoxin (TTX), an inhibitor of neural transmission, and blockade of nitric oxide (NO) synthesis. These findings have led to the proposal that SP evokes secretion in the rat colon by a sequential activation of NK-1 and NK-2 receptors and the formation of NO in a complex enteric neural reflex. The $I_{sc}$ response in the mucosa of the guinea pig colon is mediated by NK-1 receptors. The prominence of NK-1 receptor actions differentiates the guinea pig colon from the rat colon, in which all three tachykinin receptors act to increase $I_{sc}$.

These observations and others have given rise to the concept that stimulation of MP and SMP neurons that innervate the mucosa of the guinea pig small intestine releases SP and NKA within the enteric ganglia, activating VIP-mediated secretomotor pathways, and within the mucosa, stimulating epithelial cell secretion directly. This conclusion is supported by experiments showing that SP desensitization, SP immunoneutralization, and NK-1 receptor antagonists inhibit the increase in $I_{sc}$ caused by electrical field stimulation of the guinea pig small intestinal and colonic mucosae. Thus, it is clear that SP influences the secretory activity of the small intestine and colon by switching function from net absorption to net secretion of fluid and electrolytes. As discussed below, there is also increasing evidence that SP-stimulated intestinal secretion may play a role in various intestinal inflammatory diseases.

Substance P has also been demonstrated to reduce basal and hormone-stimulated bile output and to increase digestive enzyme secretion from the exocrine pancreas, but the physiological significance of these actions is unknown.

## INTESTINAL INFLAMMATION

One of the sources of SP in the gastrointestinal tract is primary afferent neurons, which have cell bodies in the

dorsal root ganglia (DRG) adjacent to the spinal cord. A subset of these sensory neurons express SP as well as other neurotransmitters (such as CGRP) and are sensitive to the excitotoxin, capsaicin. Many observations in recent years have supported the concept that these extrinsic sensory neurons expressing SP are involved in both conveying nociceptive information to the spinal cord and in regulating the inflammatory and immune responses in the peripheral tissues they innervate, including the gut. Thus, SP released by extrinsic sensory neurons in response to peripheral tissue damage may signal pain in the spinal cord (eventually resulting in pain perception centrally) and may also participate in regulating inflammation, immune responses, and, ultimately, wound healing in the affected peripheral tissue. In this set of responses, the same system (primary afferent neurons) that innervates the entire body (except the brain) is also involved in sensing tissue damage (using the pain response to avoid further damage) and in initiating repair responses such as inflammation and wound healing. In this scenario, acute inflammation is adaptive because it is an initial step in wound healing. However, in susceptible individuals, the inflammation may become chronic, for unknown reasons, resulting in debilitating chronic inflammatory bowel diseases (IBDs) such as Crohn's disease (CD) and ulcerative colitis (UC) in the gastrointestinal tract. In addition, some acute inflammatory conditions in the gut, such as pseudomembranous colitis, appendicitis, and cholecystitis, often require medical intervention because of the intensity of the inflammation.

Animal studies support the conclusion that SP released from DRG fibers innervating the intestinal mucosa plays a significant role in intestinal inflammation. In rats, NK-1 receptor antagonists have been shown to inhibit intestinal inflammation in both acute and chronic inflammation models. Pretreatment with neurotoxic doses of capsaicin to eliminate SP-expressing primary sensory afferent neurons also inhibits acute intestinal inflammation in the rat intestine; acute treatment with excitatory intraluminal doses of capsaicin elicits inflammation. In addition, targeted deletion of the gene encoding the NK-1 receptor in mice also strongly inhibits acute intestinal inflammation. These observations have given rise to the concept that inflammatory agents in the gut somehow activate capsaicin-sensitive primary sensory nerves in the mucosa, resulting in local SP release that subsequently is involved in stimulating an inflammatory cascade. Substance P is well known to cause activation of immune system cells, to increase permeability of the vascular endothelium (resulting in plasma extravasation), and to stimulate leukocyte chemotaxis.

Although it is not known if SP is involved in acute or chronic gastrointestinal inflammation in humans, indirect evidence exists supporting this concept. Tissue levels of SP have been shown to be both higher and lower than normal in UC and CD. These discrepancies may reflect tissue sampling in different phases of the disease process or other factors. In addition, changes in tachykinin receptor binding in UC and CD have been examined in detail. Examination of several neurotransmitter and hormone receptors has revealed that only NK-1 receptor binding is significantly affected in surgically resected specimens of IBD tissue. In tissue from both UC and CD patients, NK-1 receptor binding is dramatically increased. The increased NK-1 receptor binding occurs in arteriolar endothelium and in lymph nodules, sites of activation of inflammatory and immune responses. Neurokinin-2 receptor binding is not different in normal control versus IBD tissue, and NK-3 receptors are not detected in the human intestine.

To assess whether the increased NK-1 receptor binding is restricted to chronic gut inflammatory conditions, appendix tissue from patients with appendicitis, negative appendicitis (in which the patient presents with the symptoms of appendicitis but pathological analysis indicates the surgically resected tissue is normal), and normal controls were analyzed as representative of acute gut inflammation. In normal appendix, similar to normal colon, low levels of NK-1 receptor binding are observed in the circular layer of smooth muscle of the muscularis externa. In the inflamed appendicitis tissue, additional NK-1 receptor binding sites are evident in small arterioles and lymph nodules in the appendix. Interestingly, the negative appendix tissue also shows additional NK-1 binding sites associated with blood vessels and lymph nodules, suggesting that increased NK-1 receptor binding occurs prior to the infiltration of mononuclear inflammatory cells characteristic of the inflamed appendix. Whether SP and NK-1 receptors initiate the inflammatory changes in IBD and appendicitis as they do in animal models of chronic and acute intestinal inflammation is unknown, but the data from the negative appendicitis cases suggest that NK-1 receptors may indeed mediate the plasma extravasation and infiltration of mononuclear inflammatory cells observed in these diseases.

## CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

Cancer patients treated with chemotherapeutic agents often suffer from acute and/or delayed nausea and vomiting (emesis) caused by the chemotherapy drug. The

cornerstone of current antiemetic therapy consists of treatment with a serotonin (5-hydroxytryptamine; 5-HT) type 3 receptor (5-HT3) antagonist. The combination of a 5-HT3 antagonist and a corticosteroid such as dexamethasone is the standard of care for cancer patients receiving moderate to intense chemotherapy. These agents appear to exert their antiemetic actions at peripheral sites in the body. When this treatment is optimized, a majority of cancer patients receiving chemotherapy experience no emesis during their treatment. However, incompletely controlled nausea and vomiting is a significant problem for a minority of patients, such as those undergoing high-dose chemotherapy regimens and those developing emesis more than 24 hours after chemotherapy (delayed emesis). In these patients, 80–95% suffer from nausea and vomiting in the 7 days following the start of chemotherapy despite the use of standard antiemetic treatment.

It is clear that more effective antiemetic treatments are needed. In animal studies conducted in the mid-1990s, it was found that injection of SP induces emesis and that treatment with NK-1 receptor antagonists inhibits emesis. In fact, compared to 5-HT3 receptor antagonists, NK-1 receptor antagonists inhibited a much broader spectrum of emetic stimuli, including morphine, apomorphine, nicotine, copper sulfate, ipecac, radiation, cyclophosphamide, cisplatin, motion, and anesthesia. The NK-1 receptor antagonists also differed from the serotonin receptor antagonists in their site of action by acting in the central nervous system, presumably to antagonize the actions of endogenously released SP. Another advantage of NK-1 receptor antagonists over serotonin receptor antagonists relates to the activity of these agents in acute versus delayed emesis. The primary activity of the serotonin receptor antagonists has been observed on acute emesis in animals and humans, with little effect on cisplatin-induced delayed emesis. In contrast, NK-1 receptor antagonists exhibit activity in both acute and delayed emesis.

In early clinical trials, NK-1 receptor antagonists proved to be safe and effective in preventing acute cisplatin-induced nausea and vomiting, although when used alone they may be no more active than the 5-HT3 receptor antagonists. When an NK-1 receptor antagonist is combined with a 5-HT3 receptor antagonist and dexamethasone, control of acute cisplatin-induced emesis is improved by 20–30% over that obtained with the combination of a 5-HT3 receptor antagonist and dexamethasone without the NK-1 receptor antagonist. Most significantly, complete control of cisplatin-induced delayed emesis is better by 30–40% when using the triple drug combination compared to placebo.

It is clear that additional clinical trials are necessary to determine the potential value of NK-1 receptor antagonists in treating chemotherapy-induced nausea and vomiting. The early findings are very promising and it is likely that NK-1 receptor antagonist therapy in some form will find a place in the future treatment of these conditions.

## SUMMARY

The known physiological actions of SP in the gut include a role in peristalsis in the small intestine and colon and the stimulation of salivation. Although less well studied, SP may also prove to be important in esophageal motility, pepsinogen secretion, gallbladder contraction, intestinal secretion, bile output, and pancreatic secretion, but the physiological significance of these actions has yet to be determined.

## See Also the Following Articles

**Colitis, Ulcerative • Crohn's Disease • Emesis • Enteric Nervous System • Gastric Motility • Nausea • Parasympathetic Innervation • Pepsin • Salivary Glands, Physiology • Vasoactive Intestinal Peptide (VIP)**

## Acknowledgments

This work was supported by NIH Grant DK-50265 and by a Merit Review grant from the Department of Veterans Affairs.

## Further Reading

Fong, T. M. (1996). Molecular biology of tachykinins. *In* "Neurogenic Inflammation" (P. Geppetti and P. Holzer, eds.), pp. 3–14. CRC Press, Boca Raton.

Helke, C. J., Krause, J. E., Mantyh, P. W., Couture, R., and Bannon, M. J. (1990). Diversity in mammalian tachykinin peptidergic neurons: Multiple peptides, receptors, and regulatory mechanisms. *FASEB J.* 4, 1606–1615.

Hesketh, P. J. (2001). Potential role of the $NK_1$ receptor antagonists in chemotherapy-induced nausea and vomiting. *Support Care Cancer* 9, 350–354.

Holzer, P., and Holzer-Petsche, U. (1997). Tachykinins in the gut. Part I. Expression, release and motor function. *Pharmacol. Ther.* 73, 173–217.

Holzer, P., and Holzer-Petsche, U. (1997). Tachykinins in the gut. Part II. Roles in neural excitation, secretion and inflammation. *Pharmacol. Ther.* 73, 219–263.

Maggi, C. A., Patacchini, R., Rovero, P., and Giachetti, A. (1993). Tachykinin receptors and tachykinin receptor antagonists. *J. Autonom. Pharmacol.* 13, 23–93.

Mantyh, P. W., Vigna, S. R., and Maggio, J. E. (1994). Receptor involvement in pathology and disease. *In* "The Tachykinin Receptors" (S. H. Buck, ed.), pp. 581–610. Humana Press, Totowa, New Jersey.

Pothoulakis, C., Castagliuolo, I., and LaMont, J. T. (1998). Nerves and intestinal mast cells modulate responses to enterotoxins. *News Physiol. Sci.* 13, 58–63.

# Swallowing

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cricopharyngeous Striated muscle attached to the posterior aspect of the lamina of the cricoid cartilage; it forms the major component of the upper esophageal sphincter.

pharyngeal swallow Reflexive swallows independent of volitional control largely responsible for clearance of residual gastric refluxate and swallowed contents.

**Swallowing, or deglutition, is a highly coordinated activity that results in the transport of food and secretions from the oral cavity into the stomach via the esophagus. Since the respiratory and digestive tracts cross in the pharynx, the deglutitive sequence includes mechanisms that prevent aspiration of swallowed contents into the airway. As a result, with swallowing, respiration is suspended and a conformational change occurs in the structure of the oropharynx from a primarily respiratory pathway to a digestive pathway. An intricate network of neuromuscular signals controls the complex deglutitive process.**

## INTRODUCTION

Initiation of a swallow may be volitional or reflexive. Once initiated, however, every swallow leads to a predictable, involuntary sequence of events during which the bolus clears the pharynx and is transported to the stomach. On average, an individual swallows once per minute, usually to clear secretions, and approximately 1000 times per day, not including swallows with meals. Since the entire oropharyngeal component of the swallowing process takes less than a couple of seconds, evaluating this sequence has in the past been difficult. With the recent advent of newer imaging technologies, a greater understanding of this complex process is being obtained. Normal deglutition is composed of four phases: the preparatory phase, the oral phase, the pharyngeal phase, and the esophageal phase.

## OROPHARYNGEAL STRUCTURES

Many oropharyngeal structures take part in the deglutitive process. Figure 1 depicts the various muscles and surrounding tissues that are involved in the swallowing process. A total of 30 paired striated muscles and 6 pairs of cranial and cervical nerves participate in oropharyngeal swallowing. Deglutitive muscle groups are attached to cartilage (i.e., epiglottic, arytenoid, cricoid, thyroid) and the hyoid bone to provide a conduit for bolus transit and to close the airway during swallowing. The tongue is the most important muscle in the preparatory and oral phases of swallowing. In the pharynx, various groups of muscles combine to perform actions that propel the bolus through the esophagus and prevent aspiration or nasal regurgitation. The intrinsic muscles of the pharynx, the superior, middle, and inferior constrictors, are largely responsible for a peristaltic wave that aids bolus transport to the esophagus and clears the pharynx of residue. The upper esophageal sphincter is composed of a group of muscles that prevent gastric refluxate from entering the oropharynx. The cricopharyngeus is the major muscle of the sphincter along with the inferior pharyngeal constrictors, the most proximal part of the esophagus, and the thyropharyngeus, all of which maintain tonic contraction of the sphincter at rest. Protection of the airway from aspiration is achieved by closure of the larynx, as the upper esophageal sphincter is opened.

## NEUROLOGIC PATHWAYS

Much has been discovered about the central and peripheral neural pathways of deglutition in the past several years. The major components of the neural control of swallowing include sensory afferent and motor efferent fibers, located in the cranial nerves, and central organizing centers, located in the brainstem.

Sensory afferents are carried by branches of the glossopharyngeal (IX) and vagus (X) nerves to the nucleus tractus solitarius in the medulla. These fibers also carry sensory information from pulmonary stretch receptors and chemoreceptors located in the carotid and aortic bodies. This common neural pathway allows for control of respiration during deglutition. Afferent stimulation of receptors in the oropharynx is capable of initiating an automatic or reflexive/pharyngeal swallow, independent of volitional control. The pharyngeal swallow appears to be an important mechanism for pharyngeal

 

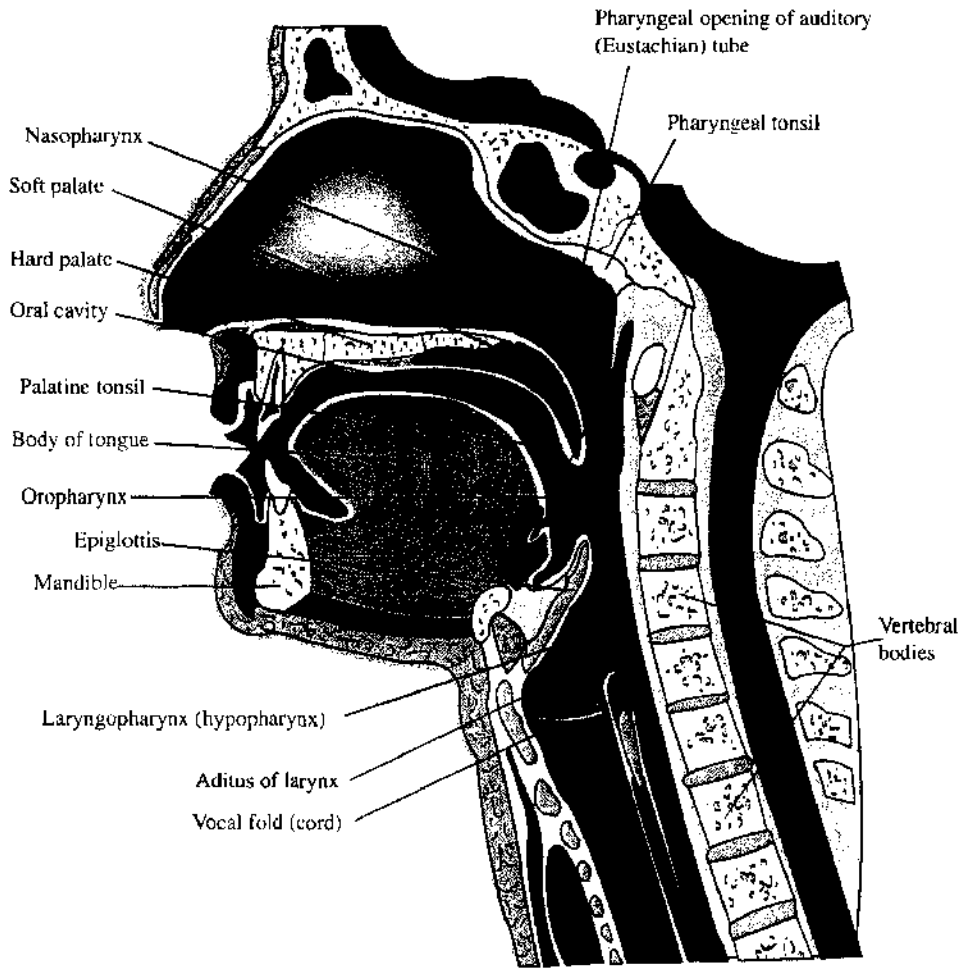


**FIGURE 1** Muscles and surrounding tissues involved in the swallowing process.

clearance for airway protection. Stimulation of the superior laryngeal nerve is most effective in producing a swallow, followed by the glossopharyngeal nerve. Other mechanoreceptors on the tongue, soft palate, and tonsillar pillars are also able to initiate a swallow if mechanically stimulated by liquid.

The brainstem plays an important role in deglutition. The motor nuclei of the cranial nerves innervating the pharyngeal muscles are located in the pons and medulla. These include the motor nuclei of the trigeminal (V), facial (VII), glossopharyngeal (IX), and vagus (X) nerves. Although stimulation of the individual nuclei will result in contraction of the various deglutitive muscles, they alone are unable to initiate the swallow reflex. Concurrent stimulation of multiple sensory afferents and summation of sensory inputs to interneurons above these nuclei, which coordinate this activity, are required. Central paired swallowing centers are located in the medulla oblongata. These poorly defined areas include the nucleus tractus solitarius, ventromedian reticular formation, and the nucleus ambiguous and are responsible for processing afferent sensory signals and programming the motor swallowing sequence. This area also receives cortical input for volitional control of deglutition.

Recent studies have shown that cortical inputs have a significant influence on the brainstem swallowing centers and a complex network of interneurons coordinates neuromuscular activity between these two levels of neuronal function. Functional magnetic resonance imaging has demonstrated cortical activation in the anterior cingulate gyrus, the motor/premotor cortex, the insula and occipital/parietal lobes in Brodmann's areas 7, 19, and 31 with deglutition. These areas, however, are not unique to deglutition and also are activated in nondeglutitive oral actions.

## PHASES OF DEGLUTITION

### Preparatory and Oral Phases

When an individual takes in food, the food is broken down mechanically by the muscles of mastication

and chemically by salivary secretions, into a bolus that is transportable by the tongue to the oropharynx during the preparatory phase. The subsequent oral phase is involved in the transfer of the bolus from the oral cavity to the pharynx. The tongue is the major muscle involved in this phase of deglutition and is able to adapt its shape and propulsive force depending on the size of the bolus. Sequential squeezing of the tongue against the hard and soft palate generates a peristaltic pressure wave that propels the bolus from the oral cavity to the pharynx.

## Pharyngeal Phase

The pharyngeal phase lasts less than 1 s; however, it is extremely complex and largely reflexive. Since the respiratory and digestive tracts cross in the pharynx, respiration is stopped during the pharyngeal swallow. Although the exact triggers of the pharyngeal swallow are not known, it usually starts as the bolus is being transported by the tongue to the pharynx, presumably by stimulation of oropharyngeal receptors of the superior laryngeal nerve. Studies have shown that although this may be true with direct stimulation of the various oropharyngeal structures, in the process of normal eating, food often enters the pharynx prior to initiation of a swallow, suggesting that either volitional control may override this stimulus or a summation of sensory input will inhibit this reflex. Alternatively, the pharyngeal phase during normal eating can be triggered as part of a seamless centrally initiated stereotyped sequence without the need for peripheral input. Figure 2 illustrates the pharyngeal phase of swallowing during evaluation with an oropharyngeal esophagram.

Swallows have been categorized as primary, when they are volitional, or secondary, when they are reflexive (i.e., without voluntary control). These secondary swallows have been referred to as pharyngeal swallows. In general, they have the same biomechanics and characteristics as primary swallows, except for the fact there is no sequential contact of the tongue with the hard palate. It is believed that these secondary swallows are important for clearing the hypopharynx of any residue or refluxate from the stomach. Pharyngeal swallows can be triggered by stimulation of many areas of the oropharynx, including the anterior faucial pillars, posterior tongue, epiglottis, posterior pharynx, and larynx. The threshold for mechanical stimulation increases with age and this may in part explain why older patients are at increased risk for oropharyngeal dysphagia and aspiration.

Once the tongue has moved the bolus to its base by lingual peristalsis, multiple well-coordinated events take place virtually simultaneously. The goal of these motor activities is to change the pharynx from a respiratory vessel to a digestive vessel, while preventing aspiration into the airway. Laryngeal closure appears to be the first event that occurs. The larynx is elevated and closed to prevent aspiration into the airway. Laryngeal closure is a stepwise process that results in first closure of the true vocal cords followed by the false cords. The epiglottis is then brought down to cover the glottic area. Studies have demonstrated that vocal cord adduction starts prior to any other deglutitive event including movement of the food from the mouth. There are four steps observed in laryngeal closure, starting with adduction of the vocal cords with horizontal approximation of the arytenoids, vertical approximation of the arytenoids to the base of the epiglottis, laryngeal ascent, and epiglottal descent. In order to prevent nasopharyngeal regurgitation, the nasopharynx is closed off by the velopharyngeal contraction and midline contraction of superior pharyngeal constrictors.

The upper esophageal sphincter is an area of high pressure between the pharynx and the esophagus. The main component of the sphincter is the cricopharyngeus muscle, with contribution of the pharyngeal constrictors and proximal esophagus. The cricopharyngeus receives innervation through the pharyngoesophageal, superior laryngeal, and recurrent laryngeal nerves and sensory input from the glossopharyngeus nerve. The upper esophageal sphincter relaxes for approximately 0.5 s with deglutition to allow bolus passage. In addition to intrinsic relaxation, the upper esophageal sphincter is opened by anterior hyoid/laryngeal traction by the suprahyoid muscles. These are the same muscles involved in laryngeal displacement and closure as described above. After the bolus is transferred to the posterior pharynx, pharyngeal peristalsis and posterior tongue thrust carry it across the upper esophageal sphincter and into the cervical esophagus. The propagated pharyngeal contraction moves from the superior, middle, and inferior pharyngeal constrictors, emptying the pharynx of any residue.

## Esophageal Phase

Once the bolus has been transferred to the esophagus across the upper esophageal sphincter, esophageal peristalsis carries it down to the stomach within a span of 6–10 s. Passage of the bolus into the proximal esophagus is followed by contraction of the upper esophageal sphincter, which initiates a progressive wave of circular muscle contraction, or peristalsis, which propels the food bolus along the esophagus. Transport of liquid is aided by gravity and liquids tend to reach the stomach

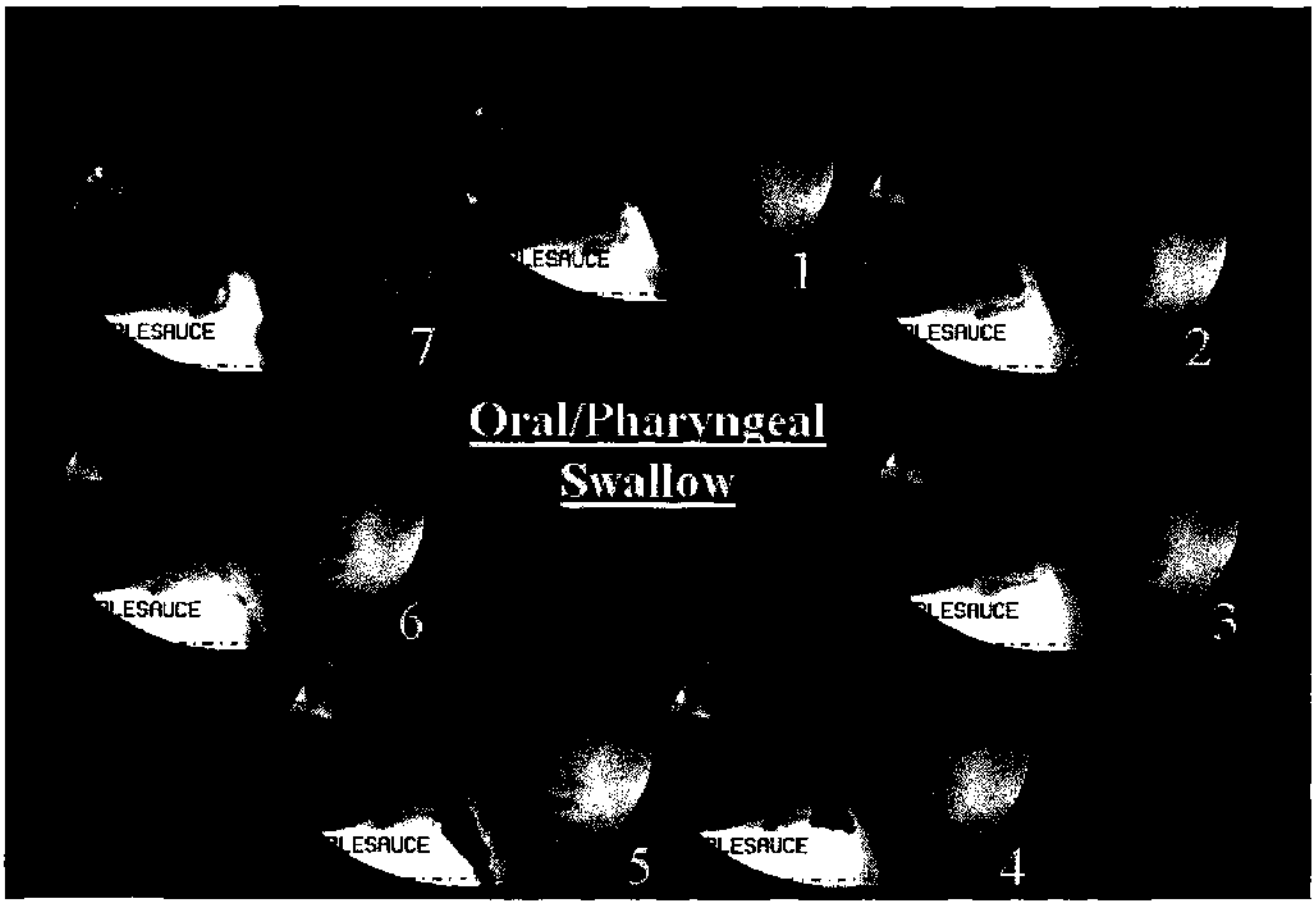


FIGURE 2 Pharyngeal phase of swallowing during an evaluation with an oropharyngeal esophagram.

prior to solids. Prior to the arrival of the bolus at the distal esophagus, the lower esophageal sphincter relaxes to allow passage of the bolus into the stomach.

## SUMMARY

The act of deglutition is a repetitive, uniform action that belies the level of complexity of its control. Since the respiratory tract and the digestive tract converge in the pharynx, airway protective mechanisms are programmed into swallowing mechanisms. Due to the many facets of neuromuscular activity that are responsible for deglutition, a wide array of medical problems can result in deglutitive dysfunction. Newer imaging modalities are now able to provide much greater insight into the swallowing process, which in turn, it is hoped, will lead to more effective therapies for people who have swallowing disorders.

## See Also the Following Articles

**Dysphagia • Esophageal Strictures • Esophagus, Anatomy • Hiccups (Singultus) • Rumination Syndrome • Sphincters**

## Further Reading

Cook, I. J., Dodds, W. J., and Dantas, R. O. (1989). Opening mechanisms of the human upper esophageal sphincter. *Am. J. Physiol.* 257, G748–G751.

Dodds, W. J. (1989). The physiology of swallowing. *Dysphagia* 3, 171–178.

Dua, K. S., Ren, J., Bardan, E., Xie, P., and Shaker, R. (1997). Coordination of deglutitive function and pharyngeal bolus transit during normal eating. *Gastroenterology* 112, 73–83.

Kahrilas, P. J. (1993). Pharyngeal structure and function. *Dysphagia* 8, 303–307.

Kahrilas, P. J., Dodds, W. J., Dent, J., Logemann, J. A., and Shaker, R. (1988). Upper esophageal sphincter function during deglutition. *Gastroenterology* 95, 52–62.

Kern, M., Birn, R., Jaradeh, S., Jesmanowicz, A., Cox, R., Hyde, J., and Shaker, R. (2001). Swallow related cerebral cortical activity maps are not specific to deglutition. *Am. J. Physiol. (Gastrointest. Liver Physiol.)* 280, G531–G538.

Lang, I. M., and Shaker, R. (1997). Anatomy and physiology of the upper esophageal sphincter. *Am. J. Med.* 103, 50S–55S.

Logemann, J. A., Kahrilas, P. J., Cheng, J., Pauloski, B. R., Gibbons, P. J., Rademaker, A. W., and Lin, S. (1992). Closure mechanism of the laryngeal vestibule during swallow. *Am. J. Physiol. (Gastrointest. Liver Physiol. 25)* 262, G338–G344.

Martin, R. E., and Sessle, B. J. (1993). The role of the cerebral cortex in swallowing. *Dysphagia* 8, 195–202.

Shaker, R. (1992). Oropharyngeal dysphagia: Practical approach to diagnosis and management. *Semin. Gastrointest. Dis.* 3, 115–128.
Shaker, R., Dodds, W. J., Hogan, W. J., and Arndorfer, R. C. (1990). Coordination of deglutitive glottic closure with oropharyngeal swallowing. *Gastroenterology* 98, 1478–1484.
Shaker, R., Ren, J., Zamir, Z., Sarna, A., and Sui, Z. (1994). Effect of aging, position and temperature on the threshold volume triggering pharyngeal swallows. *Gastroenterology* 107, 396–402.

# Sympathetic Innervation

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**paravertebral ganglia** Ganglia located alongside and parallel to either side of the vertebral column. Also known as sympathetic chain ganglia.
**postganglionic sympathetic neurons** Neurons of the sympathetic nervous system that have their cell bodies in peripheral ganglia and send axonal projections to the digestive tract.
**preganglionic sympathetic neurons** Neurons of the sympathetic nervous system that have their cell bodies in the spinal cord and send axonal projections to sympathetic ganglia in the periphery.
**prevertebral ganglia** The celiac, superior mesenteric, and inferior mesenteric ganglia of the sympathetic nervous system located in the abdomen.
**secretomotor neurons** The neurons in the enteric nervous system, which innervate the intestinal crypts of Lieberkühn to evoke the secretion of water, electrolytes, and mucus.

**The sympathetic nervous system is one of the three divisions of the autonomic nervous system that innervate the digestive tract. The other two divisions are the parasympathetic and enteric nervous systems.**

## INTRODUCTION

Neuronal cell bodies of the central nervous system component of the sympathetic innervation are positioned in the intermediolateral horn in the thoracic and lumbar regions of the spinal cord (Fig. 1). Efferent sympathetic fibers leave the spinal cord in the ventral roots to make their first synaptic connections with neurons in prevertebral sympathetic ganglia located in the abdomen. These are termed preganglionic sympathetic neurons. The prevertebral ganglia, which are the targets of the preganglionic neurons, are the celiac, the superior mesenteric, and the inferior mesenteric ganglia. Cell

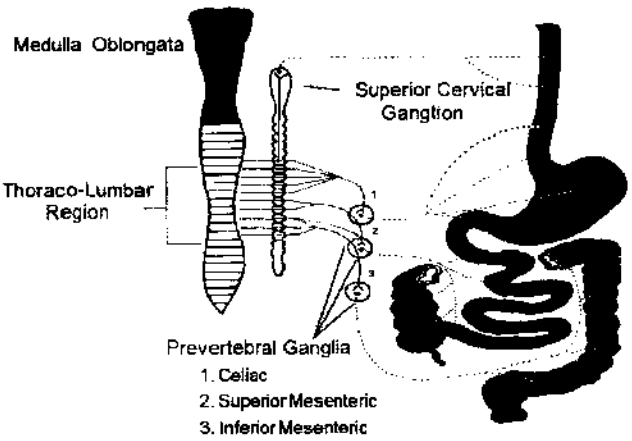


FIGURE 1 The sympathetic division of the autonomic nervous system innervates all levels of the digestive tract. Sympathetic pathways to the gut start with neurons in the thoracic and lumbar regions of the spinal cord. Efferent sympathetic fibers leave the spinal cord in the ventral roots to make their first synaptic connections with neurons in prevertebral sympathetic ganglia located in the abdomen. The prevertebral ganglia are the celiac, the superior mesenteric, and the inferior mesenteric ganglia. Cell bodies in the prevertebral ganglia project to the digestive tract, where they form synapses with neurons of the enteric nervous system in addition to innervating the blood vessels, mucosa, and specialized regions of the musculature. The upper esophagus receives innervation from the superior cervical ganglion, which is the uppermost of the paravertebral sympathetic ganglia.

bodies in the prevertebral ganglia project their axons to the digestive tract, where they form synapses with neurons of the enteric nervous system in addition to innervating the blood vessels, mucosa, and sphincteric regions of the musculature. Neurons in the prevertebral ganglia are termed postganglionic sympathetic neurons. Postganglionic sympathetic neurons express nicotinic-type receptors for acetylcholine. Preganglionic neurons release acetylcholine as a neurotransmitter in the prevertebral ganglia.

Sympathetic input to the digestive tract generally functions to shunt blood from the splanchnic to the systemic circulation during exercise and stressful environmental encounters. This occurs coincident with suppression of digestive functions, including propulsive motility and secretion.

## SYMPATHETIC NEUROTRANSMISSION

Norepinephrine released from sympathetic postganglionic neurons is the principal mediator of sympathetic actions in the gut. Norepinephrine acts directly on sphincteric muscles to increase tension and keep the sphincter closed and it also acts on the vasculature to decrease blood flow. The inhibitory action of norepinephrine at synapses in the neural control circuitry is primarily responsible for sympathetic inactivation of motility. Inhibitory action on secretomotor neurons suppresses secretion of electrolytes and water from the intestinal crypts of Lieberkühn.

The synaptic interface between the postganglionic fibers of the sympathetic nervous system and the enteric nervous system is at presynaptic $\alpha_2$ adrenoceptors. Norepinephrine released from sympathetic fibers suppresses the release of excitatory neurotransmitters at both enteric synapses and neuro-effector junctions. Suppression of synaptic transmission by the sympathetic innervation occurs at most excitatory synapses in the enteric neural networks. This inactivates the neural circuits that generate intestinal motor behavior. Activation of the sympathetic inputs allows only continuous discharge of inhibitory motor neurons to the nonsphincteric muscles. The overall effect is to suspend intestinal motility in conjunction with reduced intestinal blood flow. This state is called physiologic ileus when it occurs transiently and pathologic ileus when it persists and produces symptoms of intestinal obstruction.

### See Also the Following Articles

**Autonomic Innervation • Enteric Nervous System • Parasympathetic Innervation**

### Further Reading

Appenzeller, O. (1982). "The Autonomic Nervous System." Elsevier, Amsterdam.

Gabella, G. (1976). "Structure of the Autonomic Nervous System." Wiley, New York.

Wood, J. (1994). Physiology of the enteric nervous system. *In* "Physiology of the Gastrointestinal Tract" (L. Johnson, D. Alpers, J. Christensen, E. Jacobson, and J. Walsh, eds.). 3rd Ed., Vol. 1, pp. 423–482. Raven Press, New York.

Wood, J. (1999). "Neurogastroenterology and Motility." Milner-Fenwick, Timonium, MD.

T

# Taste and Smell

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**chemosensory systems** Biological systems that detect soluble and volatile chemicals.
**gustatory** Related to taste.
**olfactory** Related to smell.
**pheromone** Chemical that, when emitted by members of a species, will affect the behavior or physiology of other members of that species.
**taste bud** Cluster of 80–150 specialized epithelial cells; responsible for the initial events of taste reception.
**umami** Savory taste; basic taste quality elicited by monosodium glutamate.
**vomeronasal organ** Sensory organ specialized to detect pheromones in certain animals.

**Chemosensory systems, of which taste and smell are specialized forms, detect both soluble and volatile chemicals. The senses of taste and olfaction can affect social behaviors, including feeding, territoriality, and mating. Taste and smell are also used in selection and evaluation of flavor and in avoidance of potentially harmful compounds. Through the cephalic phase of digestion, taste also affects certain exocrine and endocrine secretions, thus affecting nutrition and metabolism and the overall quality of life.**

## OVERVIEW OF TASTE AND SMELL

All animals respond to various chemicals in nature; not all chemicals, however, are detected exclusively by chemosensory taste and smell systems. Painful, irritating, and pungent chemicals, for example, are also detected by the trigeminal system, and chemicals associated with sexual and social signals (pheromones) are detected by the vomeronasal organ in certain animals. Although the vomeronasal organ is physically present in humans, its functionality is controversial (see further).

Receptors for taste and olfaction are located at the entry port of each governing system, i.e., the gastrointestinal tract for taste and the respiratory tract for olfaction. Unlike other sensory systems, the taste and olfaction sensory systems have specialized peripheral chemosensory receptors that interact with the soluble and volatile chemicals that are subsequently rejected, ingested, or inhaled. Intake of chemicals can be either beneficial or harmful, and taste and smell are important discriminatory screening mechanisms for avoiding potentially harmful chemicals.

## PERIPHERAL ORGANIZATION OF THE TASTE SYSTEM

The peripheral gustatory system is exposed to a variety of physical, chemical, and biological insults. Extremely hot, cold, irritating, acidic, and nonsterile stimuli may have damaging effects on the peripheral taste receptor system. Therefore, the gustatory system evolved as a rapidly renewing specialized epithelial system. This is in contradistinction to most other sensory systems, including olfaction, in which stimuli are detected by sensory neurons.

Structures that are involved in peripheral taste reception, in decreasing order of size, are the taste papillae, taste buds, receptor cells, and taste receptor proteins. Taste papillae are visible with the unaided eye and are located throughout the oral cavity on the tongue, palate, pharynx, and epiglottis. There are four major types of gustatory papillae: circumvallate, foliate, fungiform, and taste stripes (from the original German *geschmacksstreifen*). However, the most abundant papillae on the tongue, the filiform papillae, are nongustatory (Fig. 1). These are prone to overgrowth, staining (especially with coffee and food dyes), or excessive shedding, which impart a white, coffee-brown, or raspberry appearance, respectively.

Of the gustatory papillae, the circumvallate papillae are located in a V-shaped array in the posterior third of the tongue. In humans, there are between 3 and 13 circumvallate papillae, and their number varies in other animals: rats and mice have only one, whereas cows may have as many as 25. Symmetrically located on the lateral posterior side of the tongue are the foliate papillae, which are pocket-shaped invaginations lined with taste buds. Distributed over a large surface area, the mushroom-shaped fungiform papillae cover the anterior dorsal surface of the tongue. The number of

 

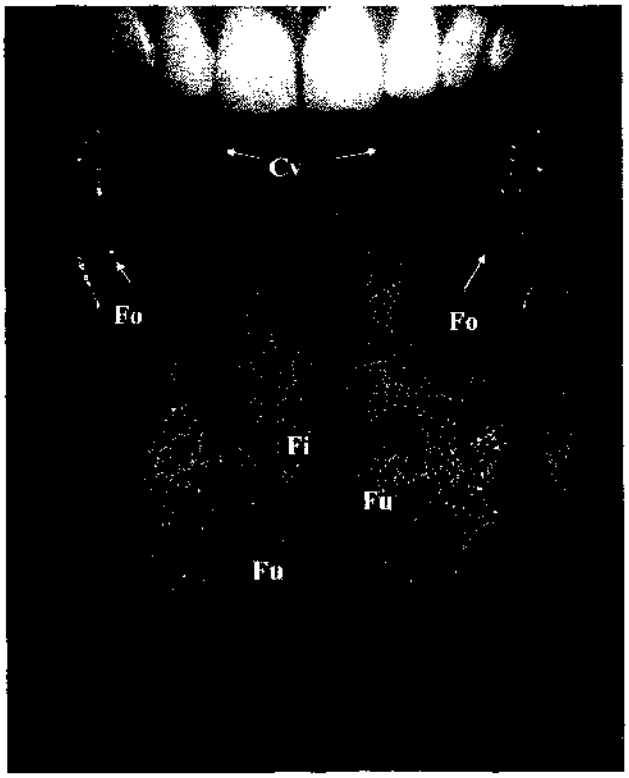


FIGURE 1 Human tongue. The dorsal surface of the tongue has four types of papillae: fungiform (Fu), nongustatory filiform (Fi), circumvallate (Cv), and foliate (Fo). Foliate papillae are not visible.

fungiform papillae in humans varies from 50 to 200. Finally, the taste stripes are located on both sides of the palatal midline at the borderline of the soft and hard palates.

The different taste papillae contain varying numbers of taste buds. For instance, in humans, the circumvallate papillae contain 100–200 taste buds, the foliate papillae have 320–2950 buds, and the fungiform papillae have 1–10 taste buds. The taste bud is the functional unit of the sense of taste. It is onion-shaped and contains 50–100 continuously maturing taste receptors and supporting taste cells (Fig. 2). Over 95% of the taste bud is shielded from the oral cavity by tight junctions, the structures that are responsible for the epithelial barrier. Only the apical portions of a few taste cells are exposed to the oral cavity through a 3- to 5-μm-wide opening, the taste pore (Fig. 3).

Unlike components of any other sensory system, taste cells have a rapid turnover rate of 10.5 days. The progenitor cells, the basal cells, are located at the base of the taste bud. As cells continuously grow and mature, they move from the basal area of the bud toward the taste pore. At any given time, the taste pore may contain the apical tips of 8–10 taste cells. The resident time of these 8–10 cells is as brief as a few hours, before they are shed into the oral cavity and washed away by saliva. This rapid turnover of cells, characteristic of many epithelial cells (e.g., certain cells lining the small intestine), means that the exposed taste receptor cells used for lunch are not the same as those used for dinner.

## TASTE RECEPTORS, SIGNAL TRANSDUCTION, AND GUSTATORY PROCESSING

Generally, gustatory stimuli interact first with specific protein receptors on the apical, exposed surface of the taste receptor cells. This interaction then leads to changes in ion flux across the taste receptor cell membrane. The resulting depolarization induces release of neurotransmitter from the receptor cell to the nerve fiber innervating the cell. Changes in the firing rate of this innervating nerve are conveyed to specific regions of the central nervous system, where the taste message is decoded into a perceptual modality. During the past 5 years, a variety of taste receptor candidates—ion channels, ligand-gated channels, enzymes, and G-protein-coupled receptors (GPCRs)—have been identified for

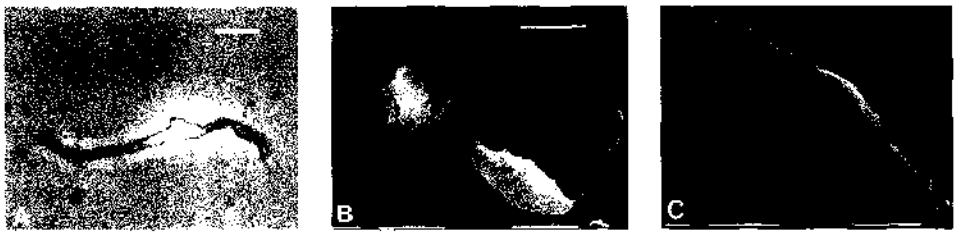


FIGURE 2 Taste cells. (A) Transmission (phase contrast) photomicrograph of a single mouse taste cell. (B and C) Scanning electron micrographs of dissociated mouse taste cells. Bars = 10 μm. Some contaminating tissue is attached to the taste cell in B. Reproduced from Spielman *et al.* (1989) with permission from Elsevier Science.

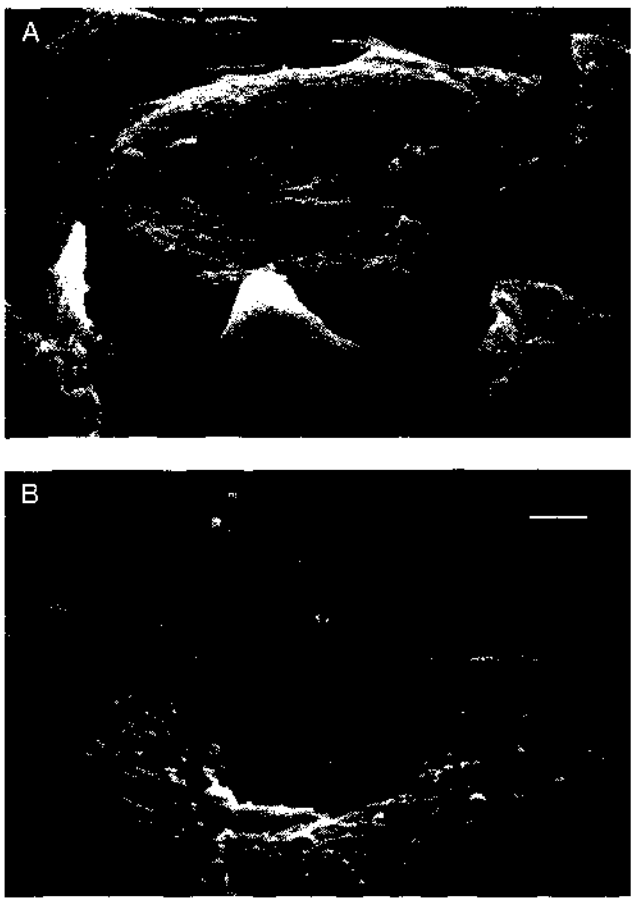


FIGURE 3 Taste pore. (A) Scanning electron micrograph of a rat fungiform papilla. The central pit represents the taste pore. (B) High-power scanning electron micrograph of the taste pore shown in A. Bar = 1 μm. Reproduced from Spielman and Brand (1997) with permission from Elsevier Science.

the five basic taste qualities: sweet, bitter, sour, salty, and savory (or umami, the amino acid taste of monosodium glutamate).

## Sweet Taste

Sweet taste in humans is elicited by a variety of compounds, including sugars and sugar derivatives, D-amino acids, some of the small L-amino acids (glycine and L-alanine), and artificial sweeteners (such as cyclamate, saccharine, aspartame, sucralose, and very high-potency sweeteners). Recent evidence suggests that GPCRs are responsible for detecting sugars. A candidate sweet receptor, the T1R3, was cloned and found to be functional only as a heterodimer with a previously cloned receptor, the T1R2. Both are expressed in about 20% of the taste cells located in the posterior, lateral, and anterior taste buds of the tongue. The mechanism by which sweet taste is transduced has been previously elucidated. T1R3/T1R2 receptors couple through an increase in cGMP and activation of a cyclic-nucleotide-gated channel that leads to depolarization through calcium influx. Interestingly, artificial sweeteners use a different pathway, similar to many bitter compounds.

## Bitter Taste

Detection of potentially harmful, even toxic, compounds is one of the primary roles of bitter taste. This gustatory stimulus is represented by a large and diverse array of compounds, ranging from ions (potassium) to complex artificial (denatonium) or naturally occurring compounds (caffeine, strychnine, quinine). Because of its potential survival benefit, bitter taste has the lowest detection threshold of all taste qualities, the largest known set of taste receptors, and is assumed to have the most diverse set of mechanisms of signal transduction.

Similar to sweet taste, bitter taste transduction involves primarily GPCRs as cell surface binding sites for many bitter stimulants. A family of 40–80 membrane-associated bitter taste receptors, termed T2Rs, was recently identified in rodents and humans. In humans, T2Rs are encoded in 24 genes located on three chromosomes. It is assumed, although not yet tested, that all T2Rs are bitter responsive. Bitter taste receptors apparently are coupled through gustducin, a taste tissue-enriched G protein α subunit, and associated β3 and γ13 subunits to the cyclic nucleotide and the phosphoinositide signal transduction pathways. Gustducin activates one or more phosphodiesterases, reducing the levels of cyclic nucleotides (cAMP and cGMP), leading to opening of a cyclic nucleotide-gated cation channel and depolarization. The β3/γ13 also activates phospholipase C-β2, which releases two second messengers, inositol trisphosphate ($IP_3$) and diacylglycerol (DAG). The former releases intracellular calcium, leading to cell depolarization. The specifics of the interplay between these two second messengers, the reduction of cyclic nucleotides, and the increase of $IP_3$ and DAG are not known; nor is it obvious which is the leading event in depolarization.

## Sour Taste

Sour taste quality, similar to bitter taste, is a protective/warning system. It indicates the protons of acids. Protons may have a local effect on oral soft and hard tissues or a systemic effect when acidity indicates spoiled food. Several protein candidates have been implicated in sour taste transduction, including amiloride-sensitive epithelial sodium channels

(ENaCs), proton-gated channels [mammalian degenerin 1 (MDEG1), $K^+$ channels], hyperpolarization-activated cyclic nucleotide-gated channels (HCNs), $H^+$-gated ion channels, and the acid-sensing ion channels (ASICs). A variety of mechanisms may be associated with these channels, indicating the potential complexity of this taste quality. Generally, all potential mechanisms lead to an increase in intracellular positive charge that results in direct depolarization. Some of these mechanisms are supported by behavioral studies using the channel blocker, amiloride, which was shown to reduce aversion to acids in some species (the hamster, for example). The specific signal transduction mechanisms for most of these receptors remain to be elucidated.

Humans have a characteristic strong facial grimace, a "sour face," when exposed to sour stimuli. The grimace induces a strong contraction of facial muscles, which channels saliva onto the surface of the tongue. The mechanisms of salivation and tasting are tightly linked, and sour taste is the strongest salivary stimulant. With increasing salivary flow rates, higher levels of bicarbonates are secreted, which leads to buffering of the acid protons, protecting oral tissue from damage.

### Salty Taste

Similar to sour taste, salty taste represents ions. Unlike sourness, however, saltiness is an essential indicator of minerals and serves as a monitor for ion homeostasis. The most important representative of this taste stimulant is sodium chloride. In rodents, an amiloride-sensitive epithelial sodium channel detects sodium chloride; the chloride appears to be mediated by a paracellular mechanism. In humans, the ENaC is less prominent and additional mechanisms not yet identified may be involved.

### Umami (Amino Acid) Taste

Umami, from the Japanese word for "delicious" (*umai*), describes a taste quality specific for monosodium glutamate (MSG). This taste is synergistically enhanced in the presence of 5′ ribonucleotides, especially inosine 5′-monophosphate (IMP) and guanosine 5′-monophosphate (GMP). MSG and glutamate, the excitatory neurotransmitter, are almost identical. It was, therefore, reasonable to expect that their receptors might be related. Indeed, a truncated form of the brain glutamate receptor, mGluR4, was found in the taste system and is one of a number of candidate receptors for umami. The signal transduction mechanism for umami using the mGluR4 receptor is assumed to be similar to that in brain, a reduction in the level of cAMP leading to a closure of an unspecified cation conductance. One problem with this mechanism is that the mGluR4 receptors are generally inhibitory. Because tasting MSG likely requires an excitatory response from the taste cell, the actual role that an inhibitory receptor such as mGluR4 plays in transduction of the taste of MSG is questionable.

A completely different receptor type for MSG has been recently proposed, one that has little homology with other known glutamate receptors. This receptor is a dimer of two of the receptor proteins of the T1R family, namely, T1R1/T1R3. Note that this dimer is similar to the proposed sweet receptor, except that one monomer of the dimer pair is different. For sweet taste, the dimer is T1R2/T1R3. One interesting feature of the T1R1/T1R3 receptor for MSG is that its activity toward glutamate is enhanced by the ribonucleotides. This synergism between glutamate and the ribonucleotides is a hallmark of umami taste, and the observation that the T1R1/T1R3 dimer is enhanced by IMP lends credence to the suggestion that T1R1/T1R3 is the major receptor for umami taste. Japanese cuisine has taken advantage of appropriate combinations of foods to maximize this synergistic effect. The combination of pork, chicken, black mushrooms, sea bream, etc., which contain nucleotides, and tomatoes, cauliflower, celery, carrots, and mushrooms, which are rich in MSG, lead to an enhanced taste for glutamate via this synergistic culinary effect.

### Other Tastes

In aquatic animals, other amino acids act as taste stimulants. The catfish, for instance, shows sensitivity to L-arginine, L-alanine, and glycine. The L-arginine receptor is a ligand-gated nonselective cation channel and is primarily located on the barbel, a tactile process located on the lip of the catfish.

Additional taste qualities exist. Fats have been recently found to act on taste cells, in addition to stimulating the trigeminal system. In particular, some free fatty acids activate taste cells through a potassium channel blockage. Water and metallic tastes have also been proposed as distinct, although nontraditional, taste qualities.

## Signal Transduction and Processing

Taste receptor cells, similar to neurons, exhibit action potentials in response to gustatory signal transduction, leading to release of neurotransmitters. The receptor cells synapse with first-order neurons at the taste bud level. Gustatory information is carried for central processing by three cranial nerves: the VIIth,

or facial (of which the chorda tympani and greater superficial petrosal branches innervate the anterior two-thirds of the tongue and palate), the IXth, or glossopharyngeal (innervating the foliate and circumvallate papillae), and the Xth, or vagus (innervating the base of the tongue, epiglottis, and pharynx). Pain and thermal and tactile information, crucial for food detection and appreciation, are carried by the maxillary and mandibular branches of the Vth or trigeminal nerve.

Although it has been assumed for many years that specific regions of the tongue are tuned for specific taste qualities, it is now clear that all three gustatory nerves carry all taste stimuli. Even single nerve fibers may be broadly tuned to carry information about multiple types of gustatory stimuli. Gustatory information carried by the three cranial nerves is passed on to the nucleus of the solitary tract in the medulla oblongata. From there, information is sent to the ventral posteromedial thalamus and eventually to the gustatory cortex in the lower tip of the parietal lobe.

## PERIPHERAL ORGANIZATION OF THE OLFACTORY SYSTEM

The sense of smell, although generally not considered as important as some of the other senses, allows human beings to detect thousands of odors in their environment. The nasal cavity is divided by the septum, and humans have three folds, or turbinates, in the dorsal part on each side. Sensory neurons are located predominantly on the superior turbinate and to a lesser extent on the middle turbinate and the septum, whereas nonsensory epithelium lines the other areas. The sensory portion of the olfactory mucosa contains several cell types. Olfactory receptor neurons (ORNs) are the cells that detect chemical stimuli. They are bipolar neurons with a dendritic process ending in an apical swelling called an olfactory knob, which is exposed to the outside world, and an axon that projects through the cribriform plate into the olfactory bulb. The olfactory knob carries either cilia or microvilli, which contain the receptor molecules that detect odors and the elements of signal transduction pathways that convert the binding of odor molecules into electrical signals. Other cells in the sensory area of the olfactory mucosa are sustentacular cells (also called supporting cells), which surround sensory neurons and produce part of the mucus that covers the epithelium and basal cells; the basal cells are immature precursor cells for ORNs and give the olfactory neuroepithelium the ability to regenerate after injury. There also is a constant turnover of ORNs, with new cells arising from dividing basal cells, then maturing into functional receptor neurons, and finally dying and being resorbed. The life span of ORNs varies but is in the range of 30 to 90 days. The nonsensory areas of the mucosa contain respiratory cells that possess motile cilia at their exposed apical ends. Ciliary movement generates a continuous retrograde flow of mucus toward the throat. Bowman glands, scattered throughout the epithelium, produce mucus. The mucus contains odorant-binding proteins, which are lipocalins, having relatively low molecular weight and high affinity for odorant molecules. Although several potential roles for odorant-binding proteins have been proposed, including transport of odorant to and/or from receptors, facilitation of odor binding to receptors, termination of receptor binding of odorant, and detoxification of the mucosa, none of these functions has been clearly established.

## OLFACTORY RECEPTORS AND SIGNAL TRANSDUCTION

To detect and distinguish thousands of different odorant molecules, the nose needs a large number of different receptors. In the early 1990s, a large family of genes that encoded apparent receptor molecules was identified in olfactory tissue. These receptors, similar to sweet and most bitter receptors, possess seven transmembrane domains that contain conserved sequences and a highly variable exposed region that is believed to be the ligand-binding site. More recently, some of these proteins have been confirmed to be odorant receptors by functional expression in cell systems such as *Xenopus* oocytes and immortalized cell lines. About 1000 different members of this family of receptors have been predicted for the mouse, one of the first and best studied mammalian models of olfaction. For humans, 350 functional olfactory receptor genes have been identified and cloned. It appears that humans have a large number of pseudogenes, which have high similarities with the nucleotide sequences encoding functional receptors but contain mutations that lead to nonfunctional proteins.

The most extensively documented signal transduction mechanism in ORNs involves the second messenger molecule cAMP. Binding of an odorant to a receptor molecule leads to the activation of a GTP-binding protein (G protein); an ORN-specific G protein, $G_{olf}$, has been identified. Activation of G proteins causes dissociation of the $\alpha$ subunit from the $\beta\gamma$ subunit complex. The $\alpha$ subunit activates the enzyme adenylyl cyclase, which converts ATP into the second messenger cAMP. cAMP in turn activates nonselective cation channels, resulting in depolarization of the receptor

neuron and leading to generation of action potentials. Calcium ions constitute a major component of the depolarizing current through the cAMP-activated channels, and the transient rise in intracellular calcium activates a second conductance through chloride channels, which amplifies the depolarization of the cell because internal chloride is unusually high in ORNs.

Several additional messenger molecules have been implicated in signal transduction in ORNs, either as part of different transduction pathways or as modulators of the cAMP cascade. These substances include cGMP, 1,4,5-inositol trisphosphate, nitric oxide (NO), and carbon monoxide (CO), although their exact contributions to signal transduction remains controversial.

## OLFACTORY BULB AND HIGHER CENTERS

Depolarization of ORNs by odors leads to the generation of action potentials, which travel along the axons that form the olfactory nerve projecting to the olfactory bulb. The axon terminals form synapses with mitral and tufted cells in the outer layer of the olfactory bulb, in discrete structures called glomeruli (Fig. 4). Mitral and tufted cells are output neurons, sending their axons to the next center in the brain. Several ORNs project onto one output neuron (convergence), and it has been shown that ORNs express only one or very few olfactory receptor molecules and that all ORNs that have the same receptors project to the same one or two glomeruli in the bulb. There are local interneurons, called periglomerular cells, that make synapses with the output neurons within a glomerulus. These dendrodendritic synapses are reciprocal, with synaptic neurotransmitter release sites on both sides of the synaptic cleft. Release of neurotransmitter from the output neuron side has an excitatory effect on the periglomerular cell, whereas release of neurotransmitter from the periglomerular cell is inhibitory to the output neurons. Activation of these synapses can result in lateral inhibition that is similar to that observed in the retina. In deeper layers of the bulb, a second population of local interneurons, the granule cells, forms the same type of dendrodendritic synapses with secondary dendrites of output neurons. The interneurons are believed to play an important role in the processing of olfactory information.

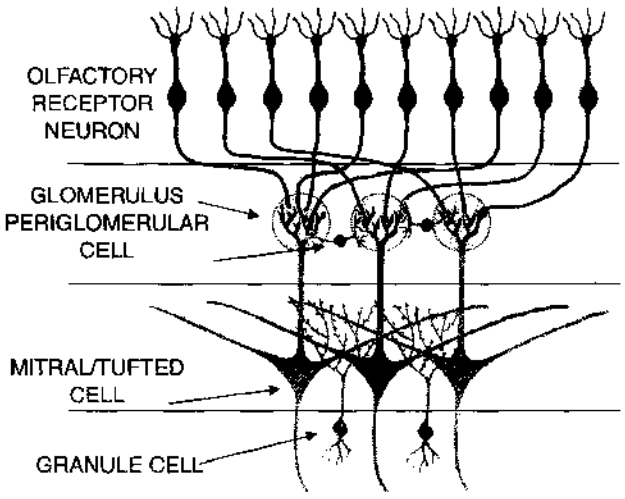


**FIGURE 4** Organization of the olfactory bulb. Olfactory receptor neurons form synapses with dendrites of mitral and tufted cells in glomeruli located in the outer layer of the olfactory bulb. Local interneurons, called periglomerular cells, make dendrodendritic synapses with mitral/tufted cells in adjacent glomeruli. Another set of interneurons, granule cells, form dendrodendritic synapses with mitral/tufted cells in the deeper layer of the bulb. The color coding illustrates the fact that receptor neurons expressing the same receptor molecules project to the same glomeruli in the olfactory bulb. Courtesy of Graeme Lowe, Monell Chemical Senses Center, Philadelphia.

The signals are finally sent via the axons of the output neurons, which form the olfactory tracts, to higher centers of the brain, including parts of the limbic system and the orbitofrontal cortex, where the integration of olfactory information with inputs from other sensory systems, including taste, takes place.

## THE VOMERONASAL ORGAN

The vomeronasal organ (VNO) is an important sensory system in many vertebrates, particularly in mammalian species (rodents, cats, and horses, among others). It is often described as the sensory system that detects pheromones, or, in a more general sense, "social odors," a notion that has been supported for several animals and stimuli. However, it is important to note that in some cases pheromone function can be exerted through the main olfactory organ and that some volatile stimuli that are not considered behaviorally relevant can be detected by sensory neurons of the VNO.

The presence of a functional VNO in humans and the existence of human pheromones are among the most intensely debated questions in the field of olfaction. Anatomical studies have described the presence of a VNO in almost all subjects, although the organ varies greatly in size and shape among individuals and even within the nostrils in an individual. Some groups have found bipolar receptor-like cells in the area of the human VNO and electrical activity has been recorded on stimulation with derivatives of human hormones. However, no evidence has been found for an axonal connection with the olfactory bulb or other parts of

the brain. Genes that show significant homology with receptor genes isolated from rodent VNOs have been identified and found to be expressed in the olfactory mucosa of humans. Although many are pseudogenes, some appear to code for a functional receptor molecule. These receptors have not yet been isolated and their ligands are unknown.

The literature contains reports of physiological effects (synchronization of menstrual cycle) as well as behavioral effects of human scents that suggest the existence of pheromone-like substances in humans, most likely associated with apocrine secretions of the skin. With a VNO that appears nonfunctional because of its lack of neuronal connections, such stimuli might be detected with the olfactory mucosa.

## INTERACTION OF TASTE, SMELL, AND OTHER SENSORY SYSTEMS

Several sensory systems must be activated to enjoy food. Gustatory, olfactory, and somatosensory (temperature, touch, and pain) systems are activated by chemical ingredients in food, dependent in part on the quality of the food. Each sensory system contributes to provide part of the overall sensation called flavor.

The absence of only one sensory system may significantly affect the pleasure of eating. For instance, individuals with an upper respiratory infection may experience a decrease in their sense of smell, and therefore a reduction in the appreciation of flavor. This can often be confused with a loss of taste. Indeed, 9 out of 10 patients complaining of loss of taste turn out to have a smell disorder. The relative ease with which the olfactory system can become compromised can be traced back to the anatomy of the olfactory system. With inhalation, the olfactory neurons, which have a slow rate of renewal, are directly exposed to potentially toxic agents. In addition, the olfactory nerve is prone to physical damage. This combination, along with frequent obstructions of the upper respiratory pathway, is a major reason why olfactory factors are the main cause of chemosensory disorders.

Texture, temperature, and carbonation (which induces mild pain) of food also affect taste and smell. The fat content of potato chips and cream cheese, the temperature of ice cream, the carbonation and temperature of beer, and the spicy nature of certain foods all contribute to the overall enjoyment of eating. Most foods are appreciated slightly below body temperature (36°C). This maximizes the emission of volatile compounds that are sensed by the olfactory system after swallowing. Other foods, such as ice cream and beer, are best at lower temperatures (closer to 4°C), whereas tea and coffee are most appreciated slightly above body temperature.

## SUMMARY

A variety of chemicals act on taste and smell. The primary binding sites for these stimuli are a large number of recently identified cell surface receptors that are coupled with diverse signal transduction mechanisms. Taste and smell interact with other sensory systems, in particular those for perceiving temperature, texture, and pain. Together, they provide an overall assessment of the chemosensory and somatosensory properties of food.

### See Also the Following Articles

**Digestion, Overview • Salivary Glands, Physiology**

### Further Reading

Adler, E., Hoon, M. A., Mueller, K. L., *et al.* (2000). A novel family of mammalian taste receptors. *Cell* 100, 693–702.

Li, X., Straszewski, L., Xu, H., Durick, K., Zoller, M., and Adler, E. (2002). Human receptors for sweet and umami taste. *Proc. Natl. Acad. Sci. U.S.A.* 99, 4692–4696.

Lindemann, B. (2001). Receptors and transduction in taste. *Nature* 413, 219–225.

Meredith, M. (2001). Human vomeronasal organ function: A critical review of best and worst cases. *Chem. Senses* 26, 433–445.

Mombaerts, P. (1999). Seven-transmembrane proteins as odorant and chemosensory receptors. *Science* 286, 707–711.

Mori, K., Nagao, H., and Yoshihara, Y. (1999). The olfactory bulb: Coding and processing of odor molecule information. *Science* 286, 711–715.

Schild, D., and Restrepo, D. (1998). Transduction mechanisms in vertebrate olfactory receptor cells. *Physiol. Rev.* 78, 429–466.

Spielman, A. I. (1999). Gustatory function and dysfunction. *Crit. Rev. Oral Biol. Med.* 9, 267–291.

Spielman, A. I., and Brand, J. G. (1997). Tongue and taste. *In* "Encyclopedia of Human Biology" (R. Dulbecco, ed.), 2nd Ed., Vol. 8, pp. 455–466. Academic Press, San Diego.

Spielman, A. I., *et al.* (1989). A method for isolating and patch-clamping individual mammalian taste cells. *Brain Res.* 503, 326–329.

# Th1, Th2 Responses

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**antigen-presenting cells** Mononuclear phagocytes, B cells, and dendritic cells. All can present antigen to major histocompatibility complex class II restricted T helper cells; which cell type presents antigen depends on where the antigen first encounters cells of the immune system.

**cytokines** Proteins produced by T cells and other immune cells; transmit signals that are important for communication among the cells of the immune system and between the cells of the immune system and other cells.

**major histocompatibility complex** Proteins encoded by the genetic loci involved in rejection of foreign or nonself tissues.

**signal transducers and activators of transcription** Proteins (Stat 1, Stat 4, and Stat 6) involved in Th1 and Th2 differentiation.

**T helper 1 (Th1) cells** Produce proinflammatory cytokines such as interferon γ and interleukin-2, which are important in macrophage activation as well as inflammatory and autoimmune reactions.

**T helper 2 (Th2) cells** Produce interleukins (IL-4, IL-5, IL-9, IL-10, and IL-13), which are involved in controlling humoral and allergic immune responses.

**Studies on T helper 1 and 2 (Th1 and Th2) cells have elucidated the processes involved in regulation and development of Th1 and Th2 cells, the cytokine production of Th1 and Th2 cells, and the effects of T cell responses in the gastrointestinal tract. Th1 and Th2 cells are characterized by the cytokines that they produce. Th1 cells are predominantly involved in cell-mediated responses and Th2 cells are predominantly involved in humoral responses.**

## INTRODUCTION

There are several subsets of T lymphocytes that are defined by their cell surface receptors. Cluster of differentiation-3 (CD3) T cell receptors, for example, function in close association with either cluster of differentiation-4 or -8 (CD4 or CD8) surface coreceptors. In addition, these CD4+ and CD8+ T cells have also been further characterized as belonging to T helper (Th1 and Th2) subsets. The development of Th1 and Th2 T cells is regulated by a number of different signaling pathways, including the interleukin-12 (IL-12) receptor signaling pathway for Th1 cells and the IL-4 receptor signaling pathway for Th2 cells. Th1 and Th2 cell subsets can largely be defined by production of subset-specific cytokines. The hallmark cytokine of Th1 cells is interferon γ (IFNγ), but Th1 cells also produce IL-2, tumor necrosis factor α (TNFα), and lymphotoxin α and β. The signature cytokine of Th2 cells is IL-4, but Th2 cells also produce IL-5, IL-9, IL-10, and IL-13. Each of these cytokine responses is associated with responses within target organs. Within the gastrointestinal tract, the Th1 response is predominantly proinflammatory. For example, Crohn's disease and intestinal graft-versus-host disease are associated with increased production of Th1 cytokines, IFNγ and TNFα. Th2 responses are important in parasitic infections in the intestine and in allergic responses, and may be antiinflammatory or selectively inflammatory in inflammatory bowel disease. For example, the cytokine profile in ulcerative colitis is characterized by increased production of the Th2 cytokine, IL-5.

## REGULATION OF TH1 AND TH2 RESPONSES

Th1 polarization is initially signaled by the T cell receptor (TCR) CD3, after its interaction with the antigen/major histocompatibility complex (MHC) on antigen-presenting cells (APCs). The second signal is produced by a number of costimulatory molecules, typified by CD28/B7. Importantly, in addition to these initiating signals, the two critical cytokines that control Th1 and Th2 differentiation are IL-12 and IL-4, respectively, though other cytokines have been reported to play a role. These two cytokines enhance the generation of their own Th subset and simultaneously inhibit the generation of the opposing subset. Th1 cells produce IFNγ and TNF, which activate macrophages but inhibit Th2 proliferation, as illustrated in Fig. 1. Th2 cells produce IL-4 and IL-5, which induce B cell activation, and IL-10, which inhibits production of IFNγ and TNF by Th1 cells.

 

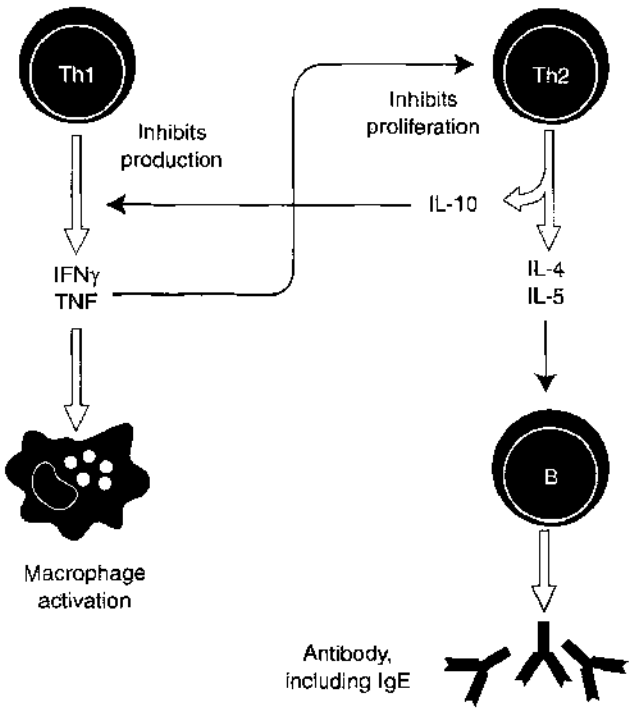


FIGURE 1 Th1 and Th2 cells produce cytokines that enhance the generation of their own Th subset and simultaneously inhibit the generation of the opposing subset. Adapted from Roitt, *et al.* (1998). "Immunology." 5th Ed, p. 125.

The critical cytokine initiating Th1 differentiation, IL-12, a heterodimeric molecule consisting of p35 and p40 subunits, is secreted predominantly by antigen-presenting cells such as dendritic cells and activated macrophages. IL-12 signaling through the IL-12 receptor (IL-12R) on the T cell induces signal transducer and activator of protein 4 (Stat 4) activation and translocation to the nucleus. Stat 4 activation induces high levels of IL-2 and IFNγ production. Importantly, not all IFNγ production by T cells is Stat 4 dependent, because Stat 6/Stat 4 double-deficient T cells produce some IFNγ, and CD8+ T cells are largely Stat 4 independent for TCR-induced IFNγ production (Fig. 2).

Another intracellular transcription factor has been recently found to be important in Th1 polarization in CD4+ T cells but not in CD8+ T cells. This factor, named T-box expressed in T cells (T-bet), was isolated using an IL-2 promoter-reporter and a cDNA library from activated Th1 cells. T-bet is a novel member of the T-box family of transcription factors. The target for T-bet is homeoprotein H1X and it seems to contribute to the capacity of T-bet to induce IFNγ production. Mechanistic studies show that overexpression of T-bet in T cells is sufficient to induce IFNγ production by direct transactivation of the IFNγ gene promoter in an IL-12-independent fashion. T-bet also up-regulates IL-12 receptor β2 chain expression on T cells (Fig. 2).

IL-1 also appears to be important in Th1 development. Differential actions of IL-1 on T cell subsets have long been recognized, and IL-1R-deficient mice display enhanced Th2 responses. IL-18, an IL-1-related factor, has been recently shown to be a selective activator of IFNγ in Th1, but not Th2, cells. Both IL-1 and IL-18 activate IL-1 receptor-associated kinase (IRAK) in Th1 cells. IRAK-deficient mice have defective IL-18-mediated Th1 type responses *in vivo*.

Importantly, IL-12 and IL-18 signaling processes appear to use distinct pathways. For example, activation of IFNγ by IL-18 has been recently found to involve activation of nuclear factor κB (NF-κB), which is the collective name for a group of transcription factors that contribute to the control of expression of many of the genes that participate in inflammation and immune responses, acting at discrete cis-acting elements in the IFNγ regulatory region. In most cells, NF-κB factors

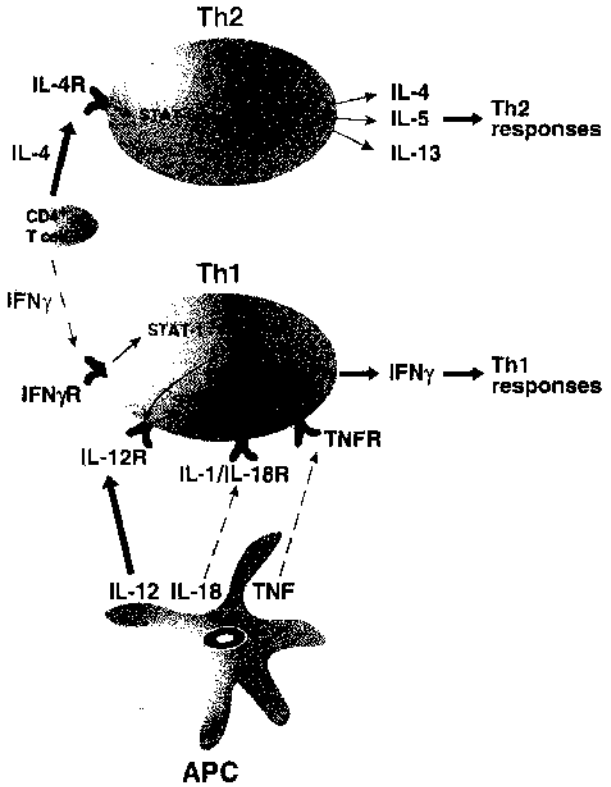


FIGURE 2 An Antigen-presenting cells (APC) and $CD4^+$ T cells secrete factors that stimulate T helper 1 and 2 (Th1, Th2) cells. IL, Interleukin; R, receptor; TNF, tumor necrosis factor; IFN, interferon; Stat, signal transducer and activator; T-bet, T-box transcription factor expressed in T cells. Adapted from Weigmann and Neurath (2002). "T-bet and mucosal Th1 responses in the gastrointestinal tract." Gut 51, 301–303.

normally occur in a latent form imposed by their association with inhibitory κB (I-κB) proteins, which dictate the cytoplasmic location of the proteins. Phosphorylation targets the inhibitor I-κB for proteasomal degradation, inducing NF-κB activation. TNF/TNF receptor (TNFR) interactions also involve the activation of NF-κB (Fig. 2).

IL-4, the critical cytokine inducing Th2 differentiation, signals through the IL-4 receptor (IL-4R) on the T cell and induces Stat 6 activation and translocation to the nucleus. Stat 6 activation induces high levels of IL-4 and IL-5. In addition, other transcription factors have been reported to affect Th2 cytokine production (Fig. 2).

## CYTOKINES INVOLVED IN TH1 AND TH2 RESPONSES

Cytokines are proteins that transmit signals that are important for communication among and between the cells of the immune system and other cells. Each cytokine has many activities and can act on several different cell types. Some cytokines activate and regulate inflammatory cells, whereas others regulate the growth, differentiation, and activation of lymphocytes and other cell types.The cytokines TNF, IL-1, IL-18, and IL-6 are regarded as proinflammatory. Th1 cytokines (IFNγ and IL-2) are important in the activation of inflammatory cells. IFNγ is well known for antiviral properties and is produced by CD4+ and CD8+ T cells. It activates mononuclear phagocytes, increases the expression of human leukocyte antigen (HLA) class I and II molecules, promotes T and B cell differentiation, activates natural killer (NK) cells and vascular endothelial cells, and enhances the respiratory burst in neutrophils. Other cytokines produced by Th1 cells are TNFα, which causes activation of macrophages, granulocytes, and cytotoxic T lymphocytes (CTLs), influences endothelial cell adhesion, and stimulates MHC class I production. Lymphotoxin α (LTα), in combination with LTβ, is important in maintenance and development of the intestinal lymphoid system.

The Th2 cytokine IL-4 is a growth and differentiation factor for B cells but also has activity as a growth factor for CD4+ T cells and mast cells. IL-4 is known to act as an immunoglobulin E (IgE) switch factor in that it selectively stimulates B cells to switch to the production of the IgE isotype. In addition, it simulates CD23 expression on mononuclear phagocytes and B cells. IL-5 is produced by CD4+ Th2 lymphocytes and influences the inflammatory response through its ability to stimulate the growth, differentiation, and degranulation of eosinophils and to act as an eosinophil chemotactic factor. IL-5 stimulates the growth and differentiation of B cells and, in the mucosal immune system, increases IgA secretion by IgA-committed B cells. IL-10 is reported to inhibit Th1 cytokine synthesis, especially in the mucosal immune system. IL-10 has been recently reported to have some immunostimulatory activities as well. IL-9 enhances T cell survival, mast cell activation, and synergy with erythropoietin. IL-13 (similar to IL-4) is produced by activated T cells and affects B cell growth and differentiation and inhibits proinflammatory cytokine production.

## GASTROINTESTINAL TH1 AND TH2 RESPONSES

Evidence that immune mechanisms are important in the initiation and the progression of ongoing tissue injury in inflammatory bowel diseases, intestinal graft-versus-host disease, food allergies, and celiac disease derives from the histologic and clinical features of these diseases as well as from laboratory studies.

### Allergic Responses and Responses to Parasitic Infection

Th2 cells and their responses are involved in many food allergies, because the Th2 IL- 4 and IL-5 cytokine responses mediate immunoglobulin switching and eosinophilic activation. A variety of hypersensitivity responses to ingested food antigens (IgE-mediated responses) have been reported and are associated with food-specific IgE antibodies. These IgE antibodies bind to high-affinity Fc receptors on mast cells and basophils as well as to low-affinity Fc receptors on macrophages, monocytes, lymphocytes, and eosinophils. When food allergens penetrate the mucosal barrier and reach IgE antibodies bound to mast cells or basophils, the cells are activated and mediators are released; this induces vasodilation, smooth muscle contraction, and mucus secretion, leading to symptoms of immediate hypersensitivity. With repeated ingestion of a food allergen, mononuclear cells are stimulated to secrete histamine releasing factors, a cytokine that interacts with IgE molecules bound to the surface of basophils and perhaps mast cells. A variety of symptoms have been associated with IgE-mediated allergic reactions: shock, urticaria, angioedema, pruritic rash, vomiting, diarrhea, nasal congestion, tongue and laryngeal edema, and wheezing.

Intestinal parasitic infections are also governed by Th1 and Th2 responses. Intestinal helminths are some of the most prevalent and successful parasites in the world. Th2 cells are important in the resistance to intestinal helminths and current data also show that a

Th1 response is associated with susceptibility. Target disruptions of Th2 cytokines, their receptors, or their signaling molecules have highlighted the importance of the Th2 response in protecting the host against parasites, in addition to the importance of the IL-4-like Th2 cytokine, IL-13. There are also indications that usual mechanisms of resistance, such as eosinophils and IgE-mediated hypersensitivity reactions, may not play as important a role as previously thought.

## Celiac Disease

Because both cell-mediated and humoral responses are thought to play a role in celiac disease, both Th1 and Th2 responses are considered important in the disease process. Gliadin and related cereal proteins are the undisputed triggers of celiac disease. In active disease, there is an increased expression and altered distribution of HLA class II DR molecules on small intestinal epithelial cells, with greater expression of HLA DR on epithelial cells in the crypt regions. This phenomenon is likely secondary to an increased Th1 cytokine response (IFNγ) by mucosal T cells. The isolation of T cell clones from affected intestinal mucosa that can be stimulated with gliadin peptides supports a role of gliadin interactions with T cells in the pathogenesis of the disease. Furthermore, investigators have demonstrated that mucosal T cells cultured with specific stimuli will exhibit Th1 features and release TNF, and TNF triggered intestinal fibroblasts to secrete matrix metalloproteinases (MMPs) that induced disruption of connective tissue. Increased focal expression of MMP-1 and MMP-3 mRNA in fibroblast cells isolated from the small intestinal mucosa of patients with celiac disease has been reported. Furthermore, specific intraepithelial lymphocytes that are up-regulated in patients with celiac disease modulate the antigen-specific immune response by secreting IL-4, which dampens the Th1 in favor of Th2 reactivation and protects the intestinal mucosa from chronic exposure to damaging agents such as dietary gluten.

On the humoral side, active celiac disease is accompanied by mucosal autoantibodies to reticulin, a common stimulator of the extracellular matrix. IgA antiendomysial autoantibodies (anti-EMAs) allow a screening test for biopsy-proved celiac disease. The role of the Th2 cells is suggested by their ability to regulate other T cell subsets and antibody-producing B cells.

## Crohn's Disease

Crohn's disease also appears to involve both Th1- and Th2-mediated responses. Importantly, patients with Crohn's disease have been noted to benefit from the inhibition of a proinflammatory Th1 cytokine TNF, and therefore Th1-mediated responses are likely very important in this disease. The inflammatory infiltrate in Crohn's disease has characteristics of an activated phenotype, likely due to a response to the same antigens over a period of time, inasmuch as there is clonal expansion of CD4+ lymphocytes in the peripheral blood. Importantly, the Th1 cytokine IL-2 mRNA is up-regulated in active CD and the T cells show a hyperreactive response to IL-2. A clinical remission occurs in patients who have fewer IL-2-secreting T cells. Furthermore, the Th1 cytokine IFNγ has been shown to be a critical initiator and perpetuator of the disease. There is a spontaneous release of IFNγ and increased IFNγ mRNA expression by lamina propria mononuclear cells and the presence of IFNγ-secreting T cells in actively inflamed mucosa. Furthermore, there is an enhanced spontaneous production of IL-12 (the critical regulator of Th1 development) in patients with Crohn's disease. IL-18 (another regulator of Th1 development) also appears to be up-regulated in Crohn's disease.

The Th2 responses mediated through IL-4 and IL-5 have also been reported in some patients with Crohn's disease. For example, there is increased production of IgG2 in the intestine, along with a massive number of plasma cells. Other studies have demonstrated an increase in production of other immunoglobulins (IgA, IgM, and particularly IgG). Recurrent Crohn's disease is associated with eosinophilic infiltration and high IL-5 mRNA levels by *in situ* hybridization. However, IL-5 production by cultured mucosal cells is decreased in Crohn's disease.

IL-10 has also been noted to play a role in Crohn's disease. IL-10 has both anti- and proinflammatory effects, depending on local concentrations of IL-10, the types of antigens present in the microenvironment, and the activation state of the immune cells in the vicinity. In the colons of some patients with Crohn's disease, there are already higher levels of IL-10 compared with controls and the mononuclear cells isolated from the ileum of patients with Crohn's disease appear to be nonresponsive to IL-10. Importantly, low ileal IL-10 concentrations have been shown to predict relapse after ileocecal resection and there is reduced IL-10 production within the activated T cell subset in patients with Crohn's disease in remission.

## Intestinal Graft-versus-Host Disease

As in many inflammatory disorders in other organs, intestinal graft-versus-host disease (GVHD) appears to

involve complex interactions among immunologic, environmental, and genetic components. T cell cytokines affect the development of GVHD. Both Th1 and Th2 cytokine-mediated occurrences of GVHD have been reported, but intestinal GVHD appears to be mediated predominantly through Th1 cytokines.

The immunopathophysiology of intestinal GVHD involves presentation of antigen to major histocompatibility complex class II disparate CD4+ T cells, which causes activation of the CD4+ T cell and induction of a Th1 cytokine profile. The proinflammatory cytokine release also causes an activation of secondary effector cells, including the macrophage, the NK cell, and the CD8+ T cell. TNF-dependent increases in membrane permeability occur early in the disease process, which likely leads to presentation of microbial products to macrophages, which further induces CD4+ Th1 cell responses in the intestine. A Th1 cytokine profile has been noted in these intestinal lymphocytes of many models of GVHD. The impetus for the Th1 polarization has been shown to involve both IL-12 and TNF. Importantly, TNF has been shown to be efficacious in the amelioration of intestinal GVHD in human trials.

## Ulcerative Colitis

The Th2 cytokine IL-5 is up-regulated in ulcerative colitis (UC), thus providing evidence that UC is mediated through these responses. Investigators have reported that IL-5 protein production is increased in cultured mucosal cells from patients with UC and that the IL-5 mRNA is elevated in biopsies from patients with UC. IL-4 mRNA has also reported to be elevated in the diseased colon of UC. Furthermore, specific antibody responses mediated by IL-4 are noted in UC but are not noted in other inflammatory diseases. Antineutrophil cytoplasmic antibodies (ANCAs) have been reported in the serum of a high proportion of patients with ulcerative colitis and sclerosing cholangitis. Moreover, the perinuclear (p-ANCA) pattern of immunofluorescent staining noted in many UC patients differs from the cytoplasmic staining seen in patients with Wegener's granulomatosis. UC patients have been reported to have a serum IgG antibody that specifically reacts with their diseased colonic tissue but not with normal colon. Importantly, specific IgG1 appears to be up-regulated in active ulcerative colitis.

## See Also the Following Articles

**Celiac Disease • Crohn's Disease • Colitis, Ulcerative • Endomysial and Related Antibodies • Food Allergy • Mast Cells • Tumor Necrosis Factor-α (TNF-α)**

## Further Reading


Fiocchi, C. (1998). Inflammatory bowel disease: Etiology and pathogenesis. *Gastroenterology* 115, 182–205.

Glimcher, L. H., and Murphy, K. M. (2000). Lineage commitment in the immune system: The T helper lymphocyte grows up. *Genes Dev.* 14(14), 1693–1711.

Hsieh, C. S., Macatonia, S. E., Tripp, C. S., Wolf, S. F., O'Garra, A., and Murphy, K. M. (1993). Development of TH1 CD4+ T cells through IL-12 produced by *Listeria*-induced macrophages. *Science* 260, 547–549.

Kaplan, M. H., Wurster, A. L., and Grushy, M. J. (1998). A signal transducer and activator of transcription (Stat)4-independent pathway for the development of T helper type 1 cells. *J. Exp. Med.* 188, 1191–1196.

Maggi, E., Parronchi, P., Manetti, R., Simonelli, C., Piccinni, M. P., Rugiu, F. S., DeCarli, M., Ricci, M., and Romagnani, S. (1992). Reciprocal regulatory effects of IFN-γ and IL-4 on the *in vitro* development of human Th1 and Th2 clones. *J. Immunol.* 148, 2142.

Parronchi, P., DeCarli, M., Manetti, R., Simonelli, C., Sampognaro, S., Piccinni, M. P., Macchia, D., Maggi, E., Del Prete, G., and Romagnani, S. (1992). IL-4 and IFN (alpha and gamma) exert opposite regulatory effects on the development of cytolytic potential by Th1 or Th2 human T cell clones. *J. Immunol.* 149, 2977.

Powrie, F., and Coffman, R. L. (1993). Cytokine regulation of T cell function: Potential for therapeutic intervention. *Immunol. Today* 14, 270–274.

Seder, R. A., Gazzinelli, R., Sher, A., and Paul, W. E. (1993). IL-12 acts directly on CD4+ T cells to enhance priming for IFN-γ production and diminishes IL-4 inhibition of such priming. *Proc. Natl. Acad. Sci. U.S.A.* 90, 10188–10192.

Zhong, Z., Wen, Z., and Darnell, J. E. (1994). Stat3 and Stat4: Members of the family of signal transducers and activators of transcription. *Proc. Natl. Acad. Sci. U.S.A.* 91, 4806–4810.

# Toxic Megacolon

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**inducible nitric oxide synthase** Key enzyme for production of nitric oxide, a potent endogenous vasodilator that acts through smooth muscle relaxation. The synthase expression is up-regulated through inflammatory processes.

**polymerase chain reaction** Laboratory method for amplification of genetic sequences from various sources (cells, plasma, feces, etc.).

**systemic inflammatory response syndrome** Systemic reaction occurring after a variety of insults, including infection, trauma, ischemia, or immune-mediated organ injury; involves one ore more of the following clinical manifestations: (a) a body temperature >38°C or 36°C; (b) a heart rate of >90 beats/min; (c) tachypnea >20 breaths/min; (d) white blood cell counts >12,000 cells/mm$^3$ or <4000 cells/mm$^3$. These physiologic changes should represent an acute alteration from the baseline in the absence of other known causes for such abnormalities.

**toxic megacolon** Dilatation of the colon during the course of fulminant colonic inflammation.

**Toxic megacolon refers to dilatation of the colon during the course of fulminant colonic inflammation, typically characterized by severe diarrhea, abdominal distension and tenderness, and total or segmental colonic dilatation without distal obstruction. This rare but potentially lethal complication of infectious colitis or inflammatory bowel disease is associated with symptoms of the systemic inflammatory response syndrome such as fever, elevation or drop in white blood cell count, anemia, tachycardia, and hypotension. The colonic dilatation that may occur in patients with Hirschsprung's disease, chronic constipation of any cause, or intestinal pseudo-obstruction is fundamentally different from toxic megacolon, in that colitis or systemic signs of systemic inflammatory response syndrome do not accompany these disorders.**

## PATHOGENETIC MECHANISMS

The term "toxic" points to the pathogenetic mechanisms underlying colonic dilatation. Whereas typical colitis is limited to the mucosal layer, toxic megacolon is characterized by inflammation extending into the smooth muscle and thereby leading to motility disturbances, including atony and various degrees of myocyte degeneration. The extent of dilatation relates to the severity and depth of inflammation and to the expression of inducible nitric oxide synthase (iNOS) in the colonic muscularis propria. iNOS may locally generate excessive amounts of nitric oxide, which is known to induce smooth muscle relaxation, and may be responsible for the colonic paralysis. In animal models, high levels of iNOS expression have been reduced by bowel decontamination with oral nonabsorbable antibiotics or administration of dexamethasone, and iNOS inhibitors prevented colonic dilatation.

## INCIDENCE

There is no reliable information on the frequency of toxic megacolon. Retrospective analyses done during the 1960s and 1970s reported a prevalence of 10 cases in 100 ulcerative colitis patients in respective centers. Based on this author's personal observations since 1990 in a European inflammatory bowel disease (IBD) referral center, the estimate is a prevalence of 1 case in 1000 patients. When analyzing the literature on toxic megacolon, it is seen that most of the knowledge that gathered since 1965 is extracted from case reports (Fig. 1). Only 30 original publications are identifiable, most of which are retrospective analyses of small diagnostic or interventional series. No prospective study has ever been published on toxic megacolon in humans. The publication frequency (and possibly also the incidence) has dropped further since 1990 (Fig. 2) and since that time, most series have dealt with various non-IBD-related causes of toxic megacolon. The tremendous improvements in IBD awareness, diagnosis, and clinical management may have made this life-threatening complication disappear and may have shifted the most common cause of toxic megacolon to infectious causes such as *Clostridium difficile*.

## ETIOLOGY

Toxic megacolon is not a specific complication of ulcerative colitis but may appear in the course of any

 

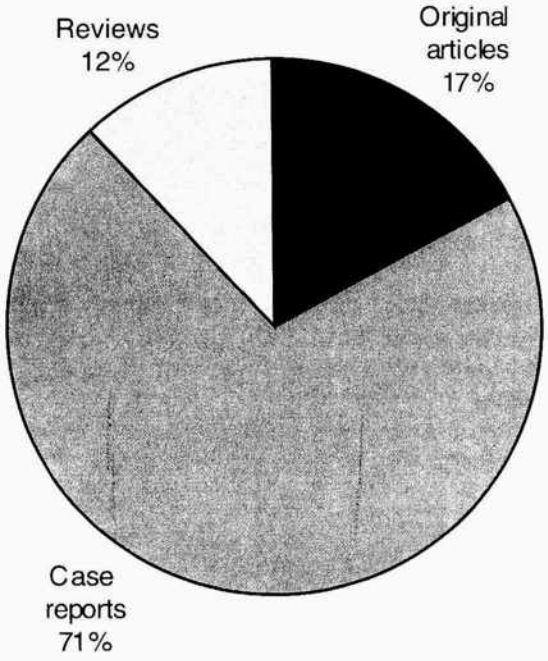


FIGURE 1 Publications on toxic megacolon between 1965 and 2001. Between 1965 and 2001, 251 articles were retrieved form the PubMed database (www.ncbi.nlm.nih.gov) using "toxic megacolon" or "toxic <and> dilatation <and> (colon <or> colitis)" as search terms. Articles with English language publication were further analyzed. Of 174 English language articles, 30 (17%) were identified as original publications, 123 (71%) were case reports, and 21 (12%) were reviews. The 30 original contributions were of a retrospective nature.

inflammatory lesion of the colonic wall, including Crohn's disease, indeterminate colitis, Behçet's disease with colonic involvement, and colitis due to ischemia (Table I). It has been learned in recent years that

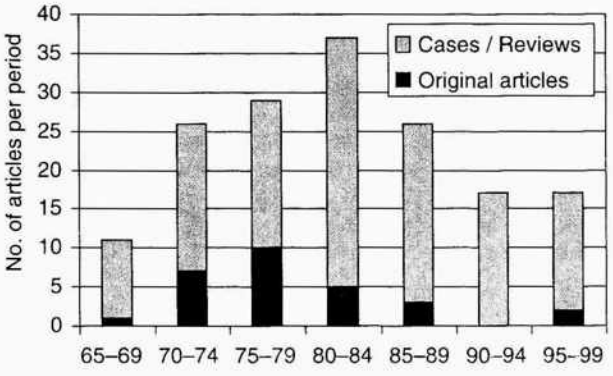


FIGURE 2 English language literature on toxic megacolon over 5-year-periods. Most of the reports on inflammatory bowel disease-associated toxic megacolon were published in the 1970s and 1980s. Notably fewer reports have been published since 1990, and most of them have dealt with various infectious causes of toxic megacolon rather than inflammatory bowel disease.

TABLE I Etiology of Toxic Megacolon

| Infectious | Noninfectious |
|---|---|
| Viral | Inflammatory bowel disease |
| Cytomegalovirus | Ulcerative colitis, |
| AIDS related (includes Kaposi's sarcoma) | Crohn's colitis, indeterminate colitis |
| Bacteria | Behçet's disease |
| *Clostridium difficile*-associated pseudomembranous colitis | Ischemic colitis |
| *Campylobacter, Salmonella, Shigella, Yersinia* | Drug induced |
| Parasitic | Chemotherapy, methotrexate, loperamide, overdose of tricyclic antidepressants |
| *Entamoeba histolytica, Cryptosporidium* | |

pseudomembranous colitis due to *C. difficile* infection is a major cause of toxic megacolon. In a retrospective evaluation from the Harvard Medical School, 21 of 710 patients with pseudomembranous colitis (3%) had required intensive care submission or even had died from this complication. Among patients with HIV infection or AIDS, cytomegalovirus colitis is the leading cause of toxic megacolon. Evidence of cytomegalovirus infection of the colon has also been found also in resected colons from patients with ulcerative colitis and toxic megacolon, perhaps implying that cytomegalovirus superinfection may be the actual cause of this complication of ulcerative colitis. Other immune-compromised patients are also at risk. AIDS-related toxic megacolon may arise from Kaposi's sarcoma of the colon or cryptosporidiosis.

## DIAGNOSTIC PROCEDURES

Patients have distension of the colon as measured on plain abdominal films (Fig. 3) and some signs of systemic inflammatory response syndrome (SIRS) (e.g., fever, tachycardia, tachypnea, or white blood cell count alteration) associated with hypotension, electrolyte imbalances, or a decreased level of consciousness. Besides plain abdominal films, computer tomography (CT) scans are appropriate for early detection of life-threatening intraabdominal complications such as colonic perforation or septic thrombosis of the portal vein. Factors thought to increase the risk of complications include procedures that increase colon trauma, such as barium enema and colonoscopy, medications that decrease gastrointestinal motility, and electrolyte imbalances. Colonoscopy, however, has been proposed for

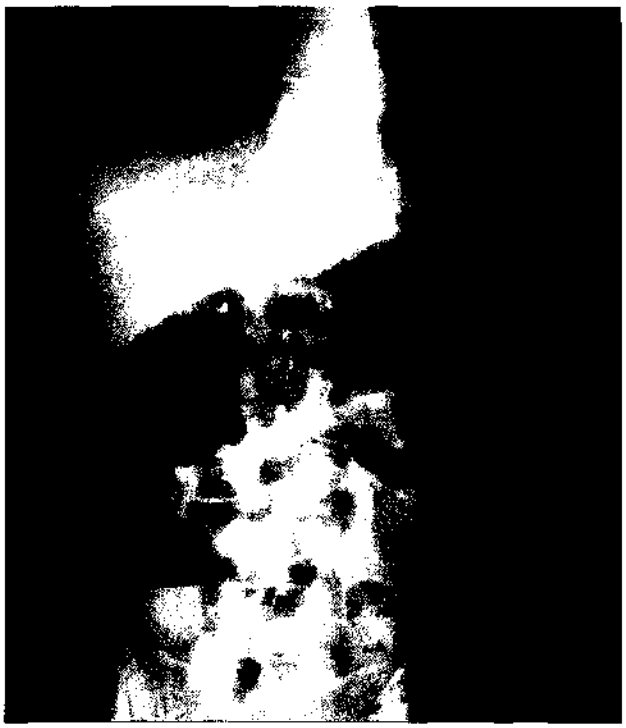

FIGURE 3 Toxic megacolon. Colonic dilatation (9 cm in the cecum, or 8 cm in the transverse colon, or 7 cm in the descending colon, or 6.5 cm in the sigmoid colon) with intraluminal air and/or fluid is typically associated with a distorted colonic contour. Courtesy of P. Pokieser, University of Vienna.

diagnostic purposes and for therapeutic decompression and may be used with caution.

The differential diagnosis of toxic megacolon is based on the patient's history (with specific consideration of inflammatory bowel diseases, AIDS, or immunosuppression) and the results of microbiological stool tests (including the detection of *C. difficile* toxin). Diagnosis of cytomegalovirus (CMV) infection may include serology, phosphoprotein-65 detection in leukocytes, and cytomegalovirus polymerase chain reaction (PCR) from plasma and feces. Timely colonoscopy, though associated with increased risk of perforation, may be crucial in patients with negative diagnostic results.

## TREATMENT

Medical management of toxic megacolon depends on the appropriate etiological diagnosis (see Table 1). Even if the diagnosis is obscure, intravenous antibiotics such as metronidazole and ciprofloxacin are safe to be initiated right after the primary diagnostic procedures. In case of *C. difficile* colitis, the offending antibiotic must be stopped and vancomycin should be added via the nasogastric tube. Antiviral therapies are indicated in cytomegalovirus colitis. Intravenous steroids are still the first-line treatment of severe inflammatory bowel disease. In severe ulcerative colitis, high-dose cyclosporine has proved helpful in avoiding emergency colectomy and should therefore be added to steroids. Though studies are lacking, infliximab may have advanced to second-line therapy in severe colonic Crohn's disease.

Patients should be monitored in the intensive care unit for fluid volume, electrolyte replacement, hemoglobin levels, and bowel distension (plain abdominal X rays every 12–24 hours). Further supportive care includes parenteral nutrition, bowel rest with nasogastric tube, and colonic decompression either by frequent "rolling" of the patient to the prone position or to the knee–elbow position or by endoscopy. Medication that slows motility should not be used.

Surgical intervention is necessary if there are signs of progressive dilatation, systemic deterioration, perforation, or hemorrhage. In the emergency setting, subtotal colectomy with Brooke ileostomy and Hartmann closure of the rectum is the procedure of choice. Surgery after colonic perforation is associated with higher mortality. It is regarded an art to find the optimal timing for such a surgical procedure. Frequent cooperative assessments of the patient's status between medical and surgical teams are the key to reduce mortality in the long run.

## See Also the Following Articles

**Behçet's Disease • Colectomy • Colitis, Indeterminate • Colitis, Ulcerative • Colonic Ischemia • Crohn's Disease • Cytomegalovirus**

## Further Reading

Beaugerie, L., Ngo, Y., Goujard, F., Gharakhanian, S., Carbonnel, F., Luboinski, J., Malafosse, M., Rozenbaum, W., and Le Quintrec, Y. (1994). Etiology and management of toxic megacolon in patients with human immunodeficiency virus infection. *Gastroenterology* 107, 858–863.

Greenstein, A. J., Sachar, D. B., Gibas, A., Schrag, D., Heimann, T., Janowitz, H. D., and Aufses, A. H., Jr. (1985). Outcome of toxic dilatation in ulcerative and Crohn's colitis. *J. Clin. Gastroenterol.* 7, 137–143.

Imbriaco, M., and Balthazar, E. J. (2001). Toxic megacolon: Role of CT in evaluation and detection of complications. *Clin. Imaging* 25, 349–354.

Mourelle, M., Casellas, F., Guarner, F., Salas, A., Riveros-Moreno, V., Moncada, S., and Malagelada, J. R. (1995). Induction of nitric oxide synthase in colonic smooth muscle from patients with toxic megacolon. *Gastroenterology* 109, 1497–1502.

Rubin, M. S., Bodenstein, L. E., and Kent, K. C. (1995). Severe *Clostridium difficile* colitis. *Dis. Colon Rectum* 38, 350–354.

Sheth, S. G., and LaMont, J. T. (1998). Toxic megacolon. *Lancet* 351, 509–513.

# Trace Minerals: Metabolism and Deficiency (Copper, Zinc, Selenium, Manganese)

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**antiport** Transport that is dependent on the countertransport of another substrate across a membrane barrier.

**cis-acting/trans-acting elements** Factors that regulate gene expression in eukaryotic cells, by the interaction of specific proteins (trans-acting elements) with specific short nucleotide sequences (cis-element motifs), usually in the promoter region of genes.

**egress** Cellular export; from the Latin *egressus*.

**initiation/elongation factors** Proteins involved in the initiation and synthesis of polypeptide chains at the level of translation.

**natural resistance-associated macrophage proteins** Novel family of proteins (Nramp1, Nramp2, and yeast proteins Smf1 and Smf2); functionally related transporters, defined by a conserved hydrophobic core of 10 transmembrane domains, that target Fe, Mn, and Zn.

**P-ATPases** Family of adenosine triphosphate-dependent metal transporters that have specificity for divalent cations.

**reactive oxidant species** Compounds derived from oxygen-mediated reactions.

**transmembrane proteins** Portions of the polypeptide chain, usually lipophilic in nature; capable of traversing the cell membrane lipid bilayer, often multiple times.

**zeta-interacting proteins** Family of metal transporters with a high avidity for zinc.

**zinc finger motifs** Structural domains associated with specific DNA–protein transcription factor interactions that are dependent on zinc for structural integrity.

**Regulatory features are important to copper (Cu), zinc (Zn), manganese (Mn), and selenium (Se) metabolism and their metabolic functions. From a nutritional perspective, normal growth, development, and many aspects of disease prevention require sustained intakes of Cu, Zn, Mn, and Se in amounts sufficient to meet the recommended daily requirements and allowances for each of these elements. The sophistication of regulatory mechanisms to maintain cellular homeostasis for Cu, Zn, Mn, and Se is in keeping with the unique and broad range of functions they perform as cofactors.**

## COPPER

### Metabolic Roles and Dietary Deficiency

Copper is essential as a redox cofactor in enzymes that usually function as oxidases. The signs and symptoms of Cu deficiency reflect perturbations in the activity of Cu-containing oxidases and range from poor energy utilization to impaired protection from oxidative free-radical damage. Specific examples include reduced cytochrome oxidase activity, defects in extracellular matrix formation, abnormal production of brain neurotransmitters, and poor iron utilization. Although Cu deficiency in humans is uncommon, experimentally induced deficiencies of Cu in animals result in anemia, defective bone development, and vascular accidents and aneurysms.

Cu deficiency is important to all aspects of growth and development. In the fetus and neonate, Cu deficiency can result in inappropriate patterns of cell death, alterations in the migration of neural crest cells, and changes in the expression of key patterning genes. These defects can be attributed to both morphological abnormalities and related epigenetic or developmental changes in DNA, e.g., in methylation patterns.

For humans, the estimated safe and adequate intake for Cu is 1.5–3.0 mg/day. This is in keeping with the requirement for optimal growth in most animals of 4–8 mg/kg of dry food or 0.5–1.0 mg per 1000 kcal (4.2 MJ). Although nutritional surveys indicate that many individuals consume 1.0 mg or less of copper per day, it is not difficult to meet the recommended level of intake given the amounts of Cu in many foods; for example, nuts, shellfish, organ meats, and legumes contain from 0.3 to 1 mg per typical serving. Condiments (various spices) and chocolate also have appreciable levels of Cu.

### Cellular Transport and Regulation

Cu uptake occurs through both high- and low-affinity transport systems. Environmental factors can influence the response to transporters. Most important are factors that influence solubility and redox state. Cu exists in two different valence states; the cupric ion ($Cu^{+}$) is the primary substrate for the transport systems that take Cu across plasma membranes. Reduction ($Cu^{2+} \rightarrow Cu^{+}$) is catalyzed by plasma membrane reductases. However, cuprous ion ($Cu^{2+}$) in the intestinal lumen is more soluble than cupric ion ($Cu^{+}$).

 

Chemical reduction of luminal contents (e.g., by reducing agents such as ascorbic acid) can decrease the amount of bioavailable Cu that may be potentially delivered to the surface of intestinal cells.

From a conceptual perspective, recent studies in yeast have shed light on proteins involved in the process of Cu transport. For example, in *Saccharomyces cerevisiae*, high-affinity Cu ion uptake has been characterized as temperature and ATP dependent. Cu ion uptake appears to be coupled with $K^+$ efflux with a 1 : 2 stoichiometry, suggesting that the process may take place via a $Cu^+/2K^+$ antiport mechanism. In yeast, the gene for Cu reductase activity, designated *FRE1*, is regulated by the Mac1 transcription factor in response to cellular Cu levels. The entry of Cu into cells is orchestrated by the action of Fre1, the Cu reductase, when Cu contacts high-affinity Cu transporters, currently designated as Ctr1 and Ctr3 (Ctr2 is a low-affinity transporter). Ctr1, Ctr2, and Ctr3 are products of *CTR* genes. High-affinity Cu uptake is facilitated by Ctr1 and Ctr3and is saturable; with a $K_m$ of 1–4 μmol/liter. Under Cu-limiting conditions, there is evidence that the transporters and proteins involved in Cu redox are up-regulated, whereas under Cu-replete conditions, they are down-regulated.

In addition to the transporters, cellular chaperones specific for Cu deliver Cu to specific cellular proteins. Other important features of Cu regulation include the role of metallothionein, a metal-binding protein for Cu, Zn, and Cd that acts to buffer abnormal shifts in the cellular concentrations of Cu, and the proteins and transporters involved in the egress of Cu from cells. Cu egress, or transport out of cells, is controlled by P-ATPase Cu transporters that are located on the surface of vesicles that arise from Golgi processing. A change in Cu status does not appear to alter Cu-transporting P-ATPase gene expression, but it does affect Cu movement to and from that outer cell membrane. Cu homeostasis must be coordinated, because the release of free Cu ions causes damage to cellular components by catalyzing the generation of reactive oxidant species (ROS).

## Systemic Regulation of Cu

From the intestine, a case can be made for the transport of Cu on albumin and in the form of low-molecular-weight complexes (e.g., histidine) to target tissues, particularly the liver. Exactly how albumin and histidine relinquish Cu to organs and tissues is currently unclear. From the liver, ceruloplasmin transports Cu to other tissues. Ceruloplasmin, the predominant Cu-containing protein in mammalian serum, is a glycosylated multi-Cu ferroxidase that carries >95% of total serum Cu. Although ceruloplasmin may function in Cu transport, the absence of ceruloplasmin has not been shown to alter Cu levels in the peripheral tissues. Such observations come from what is known about individuals and animal models that are aceruloplasminemic, a genetic disorder of ceruloplasmin deficiency. Moreover, analbuminemic rats do not have significantly impaired Cu metabolism.

The average level of Cu stored in the body ranges from 50 to 120 mg. Cu is found in all organs and tissues of the human body. In cells, Cu is always bound to proteins or to organic compounds and is not found as free Cu ions. There are higher concentrations of Cu in very young compared to adolescent or mature animals (e.g., four- to fivefold greater). The high concentration of Cu in the fetal liver is impressive; in humans, fetal liver contains 20–50 μg per gram of liver, compared to 4–5 μg per gram of liver in adults. The high levels of liver Cu in children persists for 3–5 years, followed by a decline to adult levels.

With regard to overall systemic control, under normal situations, little Cu is excreted via the kidney. Rather, Cu is excreted primarily via the bile and is released into the gastrointestinal tract with limited reabsorption. The uptake of Cu by the intestine and elimination through the bile allows Cu to be conserved and tightly regulated from a systemic perspective.

## Genetic Conditions and Cu Metabolism

The understanding of two genetic conditions, Menkes kinky-hair and Wilson disease, has contributed to the understanding of general Cu transport processes. In Menkes kinky-hair disease, there is a problem with Cu absorption and Cu transport in mesenchymal cells. In Wilson disease, there is an increased liver Cu content, leading to severe hepatic damage, followed by increased brain Cu levels and neurological lesions. Menkes disease results in pathology resembling Cu deficiency, as opposed to the pathology of Wilson disease, which resembles Cu toxicity.

Both the Wilson and the Menkes genes code for one of the P-type ATPases involved in Cu egress. In Menkes disease, the mutation in the *P-ATP-7A* gene prevents Cu transport across the basal lamina of the intestine. J. H. Menkes first described this Cu transport disorder in 1962 in a family of English–Irish descent. It was recognized immediately as an X-linked recessive disorder, characterized by retardation, impaired growth, peculiar hair, and focal cerebral and cerebellar degeneration. The condition is often lethal, with death occurring in the first or second year of life, usually from a vascular accident, i.e., aneurysm or stroke. Menkes patients also show signs of osteopenia (poor bone development) and vascular disease.

In cell culture, mesenchymal, epithelial, and neural cells from Menkes patients abnormally sequester Cu. Moreover, the ability to transfer Cu to some Cu-requiring enzymes, e.g., lysyl oxidase, is lacking or abnormal. The frequency for Menkes disease is now estimated to be about 1 in 35,000–40,000 live births among those of English–Irish descent. In contrast, Wilson disease is an inherited, autosomal recessive disorder of Cu accumulation and toxicity that occurs in about 1 of every 40,000 people. The responsible gene (*P-ATP-7B*) also codes for a vesicular membrane-bound, Cu-binding protein, but, unlike the Menkes gene, is expressed primarily in the liver. P-ATPase-7B has considerable homology to P-ATP-7A. As in Menkes disease, there are mutations in *P-ATP-7B* that account for symptoms associated with Wilson disease. Owing to its location in liver, when *P-ATP-7B* is altered by mutations, biliary excretion of Cu is impaired. An important detail is that the vesicles to which P-ATPase-7B is localized also appear to transport ceruloplasmin from cells. In cells adjacent to biliary canaliculi, some of the vesicular movement is to the cellular membrane that is exposed to the biliary canaliculus, whereas in other cells, the movement is to the cell membrane exposed to sinusoids and distensible vascular channels. It has therefore been postulated that the liver "packages" Cu for excretion into the bile by binding Cu to ceruloplasmin for release into bile or plasma. This accounts for the observations that defects in P-ATPase-7B activity often result in low levels of Cu bound to ceruloplasmin in blood and eventually failure of whole-body Cu regulation, because of hepatic accumulation of Cu.

In summary, several complex strategies are used to maintain Cu homeostasis at the cellular and organismal levels. The complexities are in part related to maintaining Cu in an appropriate redox state and the need to accommodate a diverse array of enzymatic functions. Fortunately, Cu deficiency is probably a rare occurrence, but genetic polymorphisms involving Cu transporters can occur, which mimic the signs of Cu deficiency and toxicity observed in animal models.

## ZINC

### Metabolic Roles and Dietary Deficiency

Zinc functions at the active site of many enzymes by facilitating strong, but readily exchangeable, substrate or ligand binding. Zn is not capable of redox, thus can be used biologically in novel ways at the functional sites of proteins without causing oxidative changes. Zn also plays important structural roles in proteins. One example is the zinc finger motif, the most common recurring motif in proteins that serve as transcription factors.

The importance of Zn in humans from a physiological perspective did not begin to emerge until the 1950s. Zn deficiency in animals as a cause of parakeratosis was first established. With respect to human health and disease, Zn received considerable attention when it was shown that Zn deficiency was an etiological factor in the syndrome of "adolescent nutritional dwarfism." Further work emphasized that it was particularly important to provide children with an adequate dietary Zn intake. Clinical observations in patients fed intravenously also indicated that Zn deficiency might be important to iatrogenic failure. When Zn deficiency does occur, the range of responses includes dermal lesions, poor wound healing, malabsorption, diarrhea, and immunologic defects (especially compromised T cell function).

Specific biochemical changes associated with the clinical features of Zn deficiency are not easy to identify. As a general rule, epithelial cells and cells involved in immune function are most affected by Zn deprivation. The principal biochemical lesion centers on the noncoordination of events important to the normal differentiation of cells; perhaps related to the important function that Zn plays in transcription factor integrity and structure. Of interest, there are greater changes in immune responsiveness than in changes in the activities of Zn-requiring enzymes. Zn can also have a significant impact on the hormonal regulation of cell division, specifically, the pituitary growth hormone (GH) and insulin-like growth factor-1 (IGF-1) axis. Changes in the concentrations of GH are observed in Zn deficiency, and circulating IGF-1 concentrations are consistently decreased. Other evidence suggests that reduced Zn availability affects membrane signaling systems and intracellular second messengers that coordinate cell proliferation, e.g., in response to IGF-1. Measurements of Zn concentrations in plasma are useful in identifying children who are more likely to have a growth response to Zn supplements. Regrettably, precise functional tests for Zn status are not available.

The dietary intake of Zn is around 10–15 mg/day. Sources of Zn include meat and protein-enriched foods. Factors known to influence absorption include the amount of Zn present in the intestinal lumen, and the presence of dietary promoters (e.g., human milk, animal proteins) or inhibitors (e.g., phytate, other minerals). Calcium, especially in the presence of phytate, interferes with Zn absorption.

### Cellular and Systemic Regulation of Zn

The primary site of absorption of exogenous Zn in the human is the proximal small bowel—either the distal

duodenum or proximal jejunum. Absorption studies in animal models indicate an inverse relationship between percentage of Zn absorbed and dietary Zn intake. The physiological state also affects absorption. Pregnancy and lactation can enhance absorption, which can vary from 25 to 50% depending on the dose and physiological state.

In humans, the total plasma Zn concentration is 12–25 μmol/liter, with over 90% associated with albumin, about 10% associated with α2-macroglobulin, and less than 1%, complexed to other low-molecular-weight species. Zn homeostasis is achieved largely by enterohepatic recirculation, although both the magnitude and the process differ from those for Cu. For example, a higher percentage of Zn is reabsorbed from endogenous excretion, i.e., about the same as that absorbed from dietary sources. A major source of Zn in the intestinal lumen is from pancreatic secretions, because of the importance of Zn as a cofactor for pancreatic peptidases, various hydrolases, and proteinases.

As is the case for other essential metals, several transporter systems have been identified based on corresponding homologues in yeasts. Similar to the situation for Cu, there are both high-affinity and low-affinity receptors and transporters for Zn. Further, two distinct families of zinc transporters are known: the zeta-interacting protein (ZIP) family, which imports zinc, and the ZnT family, which functions in releasing zinc or sequestering zinc internally. The ZIP transporters are found in the duodenum in the crypts and lower villi and appear available for the uptake of several metal ions, including Zn. Uptake assays demonstrate that $Cu^{+}$ and $Fe^{2+}$ can be potential substrates, because they inhibit $Zn^{2+}$ uptake, whereas $Co^{2+}$, $Mn^{2+}$, $Mg^{2+}$, and $Ni^{2+}$ have no effect on $Zn^{2+}$ uptake. The ZIP transporters are under transcriptional control based on the observation that one of the family of ZIP transporters, ZRT1, is inversely expressed relative to cellular $Zn^{2+}$ levels; $Zn^{2+}$-depleted cells have 10-fold more ZRT1 mRNA than do $Zn^{2+}$-repleted cells. There is also evidence for posttranslational regulation. When cellular Zn is elevated, there is degradation of the transporters by vacuolar proteases.

### Genetic and Other Conditions Influencing Zn Metabolism

Genetic disorders of Zn metabolism are rare. A condition known as acrodermatitis enteropathica, which responds dramatically to oral Zn supplementation, occurs in children. Acrodermatitis enteropathica is an inborn error of zinc metabolism, which is autosomal recessive. Characteristic symptoms in infancy include periorificial (oral, anal, and genital) and acral dermatitis, diarrhea, behavioral and mental changes, neurological disturbances, and secondary bacterial and fungal infections. Disorders of Zn metabolism secondary to the primary disease have also been reported in alcoholic cirrhosis, inflammatory bowel diseases, diabetes, and renal disease, although the significance of these observations in relation to Zn deprivation remains unclear.

## MANGANESE

### Metabolic Roles and Dietary Deficiency

Manganese is an essential trace element that is required for the activity of enzymes with transferase or hydrolase functions. The mitochondrial form of superoxide dismutase also requires Mn. Further, Mn deficiency is associated with perturbations in glucose metabolism, insulin function, and cholesterol regulation.

The estimated safe and adequate daily dietary intake for Mn in humans is 2–5 mg. This estimate is based primarily on dietary intake data and inferences from animal requirement studies. Regrettably, well-controlled Mn balance and excretion data are limited or have been difficult to obtain. In studies involving young adult male subjects fed conventional foods, the minimum requirement for Mn was estimated to be between 1 and 2 mg/day, an amount easily obtained in most diets. Variations in Mn intake reflect variations in food choice and the amount in the water supply (4 mg/day is defined as the lowest observable adverse-effect level, or LOAEL). Of indirect measures, serum Mn concentrations in combination with lymphocyte Mn-dependent superoxide dismutase (MnSOD) activity and blood arginase activity may have utility as indirect measures of Mn status.

Regarding excessive Mn exposure, Mn toxicity is a health risk to miners and other workers exposed to Mn-enriched dust. Excessive Mn exposure can cause impaired neurological/movement disorders. Serum Mn concentrations in combination with brain magnetic resonance imaging (MRI) scans, and neurofunctional tests seem to be the best way to monitor excessive exposure to Mn.

### Cellular and Systemic Regulation of Mn

In intestinal cell models, the uptake and transport of Mn appear controlled by saturation-type kinetics. The transport characteristics under steady-state conditions in the intestine can exhibit two components that probably reflect transcellular (carrier-mediated) and paracellular (diffusional) pathways. Calcium, calcium antagonists, ATP synthesis inhibitors, and high levels of iron decrease Mn fluxes. From the exsorption side,

the Mn flux is approximately 20-fold less than in the absorptive direction. In humans and rodent models, the absorption of Mn is decreased by phytic acid, when compared with corresponding dephytinized food components, and by high intakes, corresponding to four to five times the normal requirements. Reducing agents, such as ascorbic acid do not influence uptake.

The transport of Mn most likely involves homologues of the natural resistance-associated macrophage protein (Nramp) transporters found in yeast. In *Saccharomyces cerevisiae*, the expression of three Nramp-family transporters (Smf1p, Smf2p, and Smf3p) responds to changes in cellular Mn. In particular, Smf1p and Smf2p appear to function in Mn uptake and trafficking. Analogous to the regulation of Zn and Cu transporters, the differential regulation of Nramp transporters in yeast by Mn occurs at the level of protein stability and protein trafficking through the various secretory pathways in addition to transcriptional control. For example, Smf1p and Smf2p are degraded in cells with sufficient Mn. In contrast, Smf1p and Smf2p accumulate to high levels in Mn-deficient cells. Although the evidence suggesting Nramp transporters is inferential, much of it is very strong. As an example, animal models with iron transporter defects also have impaired Mn transport. Homozygous Belgrade rats, which have hypochromic anemia due to impaired iron transport, also have abnormalities in Mn metabolism

At present, there are few cases of Mn deficiency in the medical literature. Given the heterogeneity of the North American food supply, it is difficult to make a strong case for deficiency without involving other factors or etiologies. There may be reasons, however, to be concerned about Mn toxicity, given that intakes do exceed what are thought to be the requirements for Mn.

## SELENIUM

### Metabolic Roles and Dietary Deficiency

Selenium is of fundamental importance to human health. It is an essential component of several major metabolic pathways, including thyroid hormone metabolism, antioxidant defense, and immune function. Se is incorporated as selenocysteine at the active site of a wide range of selenoproteins. In the past two decades, over 30 new selenoproteins have been identified, of which 15 have been characterized. A number of provocative clinical studies suggest putative roles for Se in cancer protection, ROS protection, and even relationships involving viral exposure.

Plant foods are the major dietary sources of Se in most countries throughout the world. The amount of Se in soil, which varies by region, may determine the amount of Se in the food chain, wherein Se is found as selenomethionine and selenocysteine. Se is one of the few mineral elements in which the soil concentration can influence the relative amounts found in food. In the United States, the high plains of northern Nebraska and the Dakotas have the high levels of soil Se. People living in those regions generally have the highest Se intakes in the United States. Soils in central China and parts of Russia have low amounts of Se, and dietary Se deficiency is often reported in those regions. Se is also found in some meats and in seafood. Animals that eat grains or plants that were grown in Se-rich soil have higher levels of Se in muscle tissue. Some nuts, in particular Brazil nuts and walnuts, are also very good sources of Se.

The Recommended Daily Allowance (RDA) for Se is 50–100 μg in the United States and 10–75 μg in Europe. Keshan disease, also known as Se deficiency, has been observed in low-Se areas of China, where dietary intake is $<10-20$ μg/day, an intake that is significantly lower than the RDA for Se. Se deficiency has also been observed in people who rely on total parenteral nutrition (TPN) as their sole source of nutrition. The signs of Keshan disease are cardiomyopathy, increased susceptibility to infection, cataracts, and muscular lesions resulting from impaired ROS protection. There can also be loss of pigmentation in skin and hair, and, when severe, growth retardation.

Although rare in the United States, there is also a health risk of too much Se, e.g., selenosis. Symptoms include gastrointestinal upsets, hair loss, white blotchy nails, and nerve damage. The few reported cases have been associated with industrial accidents or manufacturing errors that have led to excessively high amounts of Se in supplements. The Institute of Medicine has set a tolerable upper intake level for Se at 400 μg/day.

### Cellular and Systemic Regulation of Se

Both organic and inorganic forms of Se can be utilized in the body. The order of uptake in Caco-2 cells is $SeO_3^{2-} \leq$ selenocysteine $<$ selenomethionine $< SeO_4^{2-}$. Both amino acid-related and anion transporters are involved in Se transport. Many of the details, however, have yet to be resolved. For example, the transport of selenomethionine is inhibited by its sulfur analogue, methionine, whereas inhibition of the transport of selenocysteine by cysteine is not observed. The transport of $SeO_4^{2-}$ is inhibited by thiosulfate, but not sulfate. A $Na^+,K^+$-ATPase is probably responsible for energizing the brush border transport of selenate, where the ileum is the site of absorption. A number of intestinal inflammatory diseases and short-bowel syndrome can lead to Se deficiency.

In contrast with intestinal cells, red cells in particular demonstrate selective uptake of organic forms of selenium. Of the most common Se compounds (selenate, selenite, selenomethionine, and selenocysteine), selenite injected intravenously is taken up rapidly and selectively through an anion-exchange carrier or transporter. The rapid and selective uptake of selenite by red blood cells is explained by the selective and efficient uptake through the anion-exchange carrier, followed by reduction by glutathione-requiring steps. Selenite uptake is inhibited by chromate, which promotes glutathione depletion.

Another unique aspect of Se regulation is that its insertion into protein occurs posttranslationally in the form of the amino acid, selenocysteine (SeCys). Such occurrence of this element in protein is widespread in all forms of life. Elucidating how Se is incorporated as SeCys has modified our understanding of the genetic code. The formation of SeCys with its novel codon expands to 21 the codon used for naturally occurring amino acids. Although it was recognized in the mid-1960s that the codon AUG had a dual role of initiating protein synthesis and inserting methionine at protein translation start sites, the possibility that a second codon also had two functions was not considered at the time. It is now known that UGA serves both as a termination and a SeCys codon.

SeCys can be attached to $tRNA^{Cys}$ by cysteinyl-tRNA synthetase and can be incorporated nonspecifically into protein in response to Cys codons, which is the reason why many proteins contain Se at sites other than the Se-containing active sites in selenoenzymes. However, SeCys is synthesized by a novel process. The translation of selenoprotein mRNAs requires both cis-acting and trans-acting factors. SeCys is inserted into nascent selenopeptides in mammals by means of a unique amino acid insertion system. Specific 3′ untranslated (UTR) mRNA structures, designated SECIS elements, function in recruiting SBP2, a SeCys-specific elongation factor, and selenocysteinyl-$tRNA^{Ser,SeCys}$ into the SeCys insertion complex, the selenosome. SeCys $tRNA^{Ser,SeCys}$ is used as the site for SeCys biosynthesis and for its incorporation into the active site of specific selenoproteins. Further work also suggests considerable complexity in the regulation of specific selenoenzymes, e.g., transcriptional as well as translation regulatory controls exist for glutathionine peroxidase.

## CONCLUDING COMMENTS

Although it is difficult to make a case for frank nutritional deficiencies of Cu, Zn, Mn, or Se in humans, there is a good likelihood of identifying polymorphisms that may alter an individual's need for a given element. Although perhaps obvious from a biochemical perspective, it is also important to underscore that each mineral contributes unique chemical properties that are essential to a diverse array of enzymatic and related functions. The complexities of these functions underscore the need in turn for equally complex regulatory and homeostatic controls.

### See Also the Following Articles

**Dietary Reference Intakes (DRI): Concepts and Implementation • Digestion, Overview • Malnutrition • Wilson's Disease**

### Further Reading


Bull, P. C., and Cox, D. W. (1994). Wilson disease and Menkes disease: New handles on heavy-metal transport. *Trends Genet.* 10, 246–252.

Burk, R. F. (2002). Selenium, an antioxidant nutrient. *Nutr. Clin. Care* 5, 75–79.

Burk, R. F., and Hill, K. E. (1993). Regulation of selenoproteins. *Annu. Rev. Nutr.* 13, 65–81.

DiDonato, M., and Sarkar, B. (1999). Genetic disorders of metal transport and metabolism. *In* "The Molecular Biology and Toxicology of Metals" (R. K. Zalups and D. J. Koropatnick, eds.), Chap. 6, pp. 186–208. Taylor and Francis, London.

Driscoll, D. M., and Copeland, P. R. (2003). Mechanism and regulation of selenoprotein synthesis. *Annu. Rev. Nutr.* 23, 17–40.

Eide, D. J. (2000). Metal ion transport in eukaryotic microorganisms: Insights from *Saccharomyces cerevisiae*. *Adv. Microb. Physiol.* 43, 1–38.

Eide, D. J. (1998). The molecular biology of metal ion transport in *Saccharomyces cerevisiae*. *Annu. Rev. Nutr.* 18, 441–469.

Freeland-Graves, J. H., Behmardi, F., Bales, C. W., Dougherty, V., Lin, P. H., Crosby, J. B., and Trickett, P. C. (1988). Metabolic balance of manganese in young men consuming diets containing five levels of dietary manganese. *J. Nutr.* 118, 764–773.

Greger, J. L. (1998). Dietary standards for manganese: Overlap between nutritional and toxicological studies. *J. Nutr.* 128, 368S–371S.

Guerinot, M. L. (2000). The ZIP family of metal transporters. *Biochim. Biophys. Acta* 1465, 190–198.

Harris, E. D. (2000). Cellular copper transport and metabolism. *Annu. Rev. Nutr.* 20, 291–310.

Hellman, N. E., and Gitlin, J. D. (2002). Ceruloplasmin metabolism and function. *Annu. Rev. Nutr.* 22, 439–458.

Keen, C. L., Ensunsa, J. L., and Clegg, M. S. (2000). Manganese metabolism in animals and humans including the toxicity of manganese. *Met. Ions Biol. Syst.* 37, 89–121.

Menkes, J. H. (1999). Menkes disease and Wilson disease: Two sides of the same copper coin. Parts I and II: *Eur. J. Paediatr. Neurol.* 3, 147–158; 3, 245–253.

O'Halloran, T. V., and Culotta, V. C. (2000). Metallochaperones, an intracellular shuttle service for metal ions. *J. Biol. Chem.* 18275(33), 25057–25060.

Pena, M. M., Lee, J., and Thiele, D. J. (1999). A delicate balance: Homeostatic control of copper uptake and distribution. *J. Nutr.* 129, 1251–1260.

Simpkins, C. O. (2000). Metallothionein in human disease. *Cell. Mol. Biol.* 46, 465–488.

# Transforming Growth Factor-β (TGF-β)

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growth factor A protein, usually secreted from cells, that exerts its biological activity by binding to high-affinity, cell surface receptors at low concentrations; most growth factors have diverse biological activities including actions independent of cell growth regulation.

Transforming growth factor-β (TGF-β) is a dimeric polypeptide growth factor belonging to a superfamily of related proteins. All superfamily members are distinguished structurally by a cluster of conserved cysteine residues held together by disulfide bonds. These proteins display a remarkable diversity of biological activities, including cell growth regulation, cell fate determination, immune function, and morphogenesis. TGF-β-related peptides and TGF-β receptors are synthesized by virtually all normal cells including epithelial, smooth muscle, and hematopoietic cells in the gastrointestinal tract.

## THE TRANSFORMING GROWTH FACTOR-β GENES AND PROTEINS

The mammalian transforming growth factor-β (TGF-β) family consists of three proteins with similar biological activities. These three "isoforms" are designated TGF-$\beta_1$, $\beta_2$, and $\beta_3$ and are localized to human chromosomes 19, 1, and 14, respectively. All three TGF-β proteins are first synthesized and secreted in biologically inactive, latent precursor complexes that are incapable of binding to cell surface TGF-β receptors. "Activation" of TGF-β occurs when the mature, 25 kDa biologically active form of TGF-β is liberated from the precursor complex. Activation of latent TGF-β is believed to be a major step in the regulation of TGF-β activity. Mature, biologically active TGF-β is released from the latent complex by extremes of pH, proteolysis by plasmin, and transglutaminase-dependent interaction with the extracellular matrix. A great deal remains to be learned about the normal process of TGF-β activation and how it is altered under pathophysiological conditions.

## TRANSFORMING GROWTH FACTOR-β RECEPTORS

The TGF-β receptors are designated TGF-βRI (~53 kDa), TGF-βRII (~70 kDa), and TGF-βRIII (~300 kDa). Each has an extracellular ligand-binding domain, a transmembrane sequence, and a cytoplasmic sequence. In general, all three isoforms of TGF-β bind to receptor types I, II, and III, albeit with modest differences in affinity. Binding of TGF-β to TGF-βRII recruits TGF-βRI into a tetrameric receptor complex, resulting in the transphosphorylation and activation of a serine/threonine kinase in the cytoplasmic tail of TGF-βRI. It is convenient to think of TGF-βRII as a "sensor" receptor and TGF-βRI as a "transducer" receptor. TGF-βRIIIs are abundant, but have no known signaling capability and have mostly been considered "reservoir" receptors. Regulation of receptor signaling is remarkably complex because of a large number of receptor-interacting proteins that modify signaling. These include FKBP12, the α-subunit of farnesyl transferase, TRIP-1, STRAP, and TRAP-1, among others.

## INTRACELLULAR SIGNALING BY TRANSFORMING GROWTH FACTOR-β

The main signaling proteins activated by TGF-β superfamily members are called Smads (Fig. 1), although a variety of other traditional intracellular signaling pathways are also modulated. The Smads most relevant to TGF-β signaling in the gastrointestinal tract are Smad2 and Smad3 (receptor-regulated or R-Smads), Smad4 (a common-partner or Co-Smads), and Smad6 and Smad7 (inhibitory Smads). Phosphorylation of Smad2 and Smad3 by serine/threonine kinase activity in TGF-βRI is necessary for activation of TGF-β signaling. Phosphorylation of Smad2 and Smad3 permits interaction with Smad4. This is the final configuration required for translocation of the TGF-β signal into the nucleus, where modification of gene expression occurs by binding to unique Smad-binding elements in TGF-β-responsive genes. Smad7, an inhibitory Smad, binds to activated TGF-βRI and inhibits the phosphorylation of Smad2, the assembly of Smad complexes, and the nuclear translocation of Smads.

An increasingly diverse and complex array of transcriptional activators and repressors interact with the Smad complex to modify gene transcription in the cell nucleus. These include transcriptional activators such

 

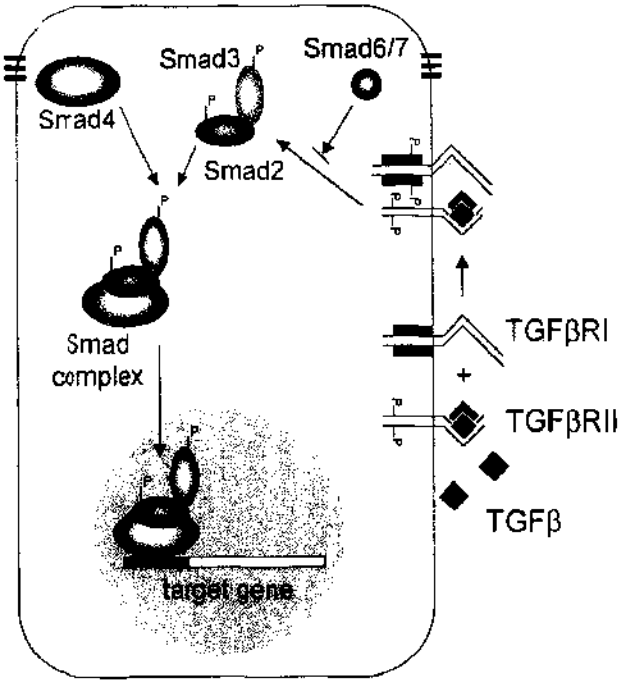


FIGURE 1 TGF-β signaling: TGF-β binds to a dimerized TGF-β type II receptor, initiating an interaction with type I receptors and phosphorylation of the cytoplasmic tail of TGF-β type I receptor, as well as Smad2 and Smad3. In concert with Smad4, the Smad complex translocates to the nucleus to modify gene expression and alter cell behavior.

as CREB-binding protein (where CREB denotes $Ca^{2+}$/cAMP-response element-binding protein)/p300 and transcriptional repressors such as SnoN, c-Ski, and TGIF. Many of these proteins secondarily interact with classical transcriptional repressors, such as histone deacetylases.

## BIOLOGICAL ACTIONS OF TRANSFORMING GROWTH FACTOR-β IN THE HUMAN GASTROINTESTINAL TRACT

TGF-β has diverse biological actions in the gastrointestinal tract, including inhibition of epithelial cell growth, stimulation of extracellular matrix (ECM) synthesis, stimulation of angiogenesis, stimulation of cell motility, and suppression of the immune system. The growth inhibitory actions of TGF-β are especially important, as their loss may result in gastrointestinal cancer. TGF-β normally arrests cell growth by causing a reversible block in the G1 phase of the cell cycle. This occurs as a result of inhibition of c-myc proto-oncogene expression and blockade of cyclin-dependent kinase activites, both of which are critical preparatory steps for DNA synthesis and cell replication. Another major biological effect of TGF-β is the modulation of genes regulating ECM deposition, which results in extracellular matrix formation. This occurs by increased synthesis of ECM proteins (collagen, fibronectin) and proteinase inhibitors (plasminogen activator inhibitor), decreased synthesis of matrix-degrading activities (plasminogen activator, collagenase, elastase), and modulation of matrix receptors and binding proteins (integrins). The effect of TGF-β on extracellular matrix synthesis appears to have major clinical significance, as a large number of fibrotic diseases, such as cirrhosis, pulmonary fibrosis, stricture, and glomerulonephritis, are associated with increased TGF-β activity. Because of its effects on the extracellular matrix, TGF-β increases wound healing, including incisional wounds in the gastrointestinal tract. The effects of TGF-β on the immune system are complex, but TGF-β is predominantly immunosuppressive. The marked inflammation observed in the gastrointestinal mucosa of TGF-β-deficient "knockout" mice underscores the importance of TGF-β in regulating the gastrointestinal immune system. Blockade of TGF-β signaling in immune cells, with resultant increased immune activity, has been proposed as an important factor in inflammatory bowel disease and autoimmune hepatitis.

## A ROLE FOR TRANSFORMING GROWTH FACTOR-β IN GASTROINTESTINAL CANCER

More than 75% of human colon and pancreatic cancers are resistant to growth arrest by TGF-β, an observation believed to be key in the causation of these tumors. For example, an inactivating mutation in the TGF-βRII gene occurs in persons with defects in DNA mismatch repair, leading to hereditary nonpolyposis colon cancer, a familial cancer syndrome with an increased incidence of gastric, endometrial, and colon cancers. Overall, these types of mutations account for approximately 15% of all colorectal cancers. An additional 6–15% of sporadic colon cancers have mutations in TGF-βRII. Inactivating mutations in Smad2 and Smad4 occur in approximately 6 and 20% of sporadic colorectal carcinomas, respectively. Smad4 mutations are found in approximately 40% of kindreds with a rare autosomal dominant disorder called familial juvenile polyposis coli. Approximately 50% of pancreatic adenocarcinomas harbor inactivating Smad4 mutations. In addition to these genetic abnormalities, resistance to TGF-β growth arrest occurs in a significant percentage of colon and pancreas carcinomas because of the presence of mutant, activated

K-Ras, an oncogene that blocks Smad signaling. Restoration of TGF-β signaling may someday be a viable option in the treatment of gastrointestinal cancer.

## See Also the Following Articles

**Cancer, Overview • Epithelium, Proliferation of • Growth Factors**

## Further Reading

Barnard, J. A. (2003). Peptide growth factors. *In* "Gastrointestinal Cancers" (A. K. Rustgi and J. M. Crawford, eds.), 1st Ed., pp. 33–54. W. B. Saunders, Philadelphia, PA.

Blobe, G. C., Schiemann, W. P., and Lodish, H. F. (2000). Mechanisms of disease: Role of transforming growth factor beta in human disease. *N. Engl. J. Med.* **342**, 1350–1359.

Kim, S. J., Im, Y. H., Markowitz, S., and Bang, Y. J. (2000). Molecular mechanisms of inactivation of TGF-beta receptors during carcinogenesis. *Cytokine Growth Factor Rev.* **11**, 159–168.

Shu, H. J., and Burgess, A. W. (2001). Regulation of transforming growth factor β signaling. *Mol. Cell. Biol. Res. Commun.* **6**, 321–330.

Ten Dijke, P., Goumans, M. J., Itoh, F., and Itoh, S. (2002). Regulation of cell proliferation by Smad proteins. *J. Cell Physiol.* **191**, 1–16.

# Transplantation Immunology

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**alloantigen** Antigenic differences between members of the same species.

**cytokines** Peptide products of activated leukocytes.

**HLA** The symbol for the major histocompatibility complex in humans.

**ligand** A structure on one cell recognized by a receptor on another cell.

**major histocompatibility complex** A closely linked series of genes that account for the strong transplantation barrier between individuals.

Transplantation immunology is a subject that examines (1) the biology of tissue and organ grafts transferred from donor sources to genetically dissimilar recipients and (2) the activity and mechanisms of the multifaceted host defenses that react against the foreign stimulus. If the resultant panoply of antigen-specific cellular and humoral events is not modified or inhibited by X-radiation or chemical or biological means of immunosuppression, they will inexorably and irreversibly destroy the graft. Understanding of the intricacies of these responses has accelerated rapidly during recent decades, with elucidation of the functions, interplay, and effects of the cascade of adhesion molecules and other inflammatory mediators, leukocyte populations, their relationship to antigens presented to them, and the influence of a variety of effector products. Indeed, understanding of the process of "rejection" of foreign tissues has evolved from the simplistic concept that specifically sensitized host lymphocytes infiltrate and directly kill the transplant, to the more refined appreciation of a sequential series of cellular and molecular events of astounding complexity.

## BACKGROUND

The basic doctrine of transplantation is that tissue transferred between different sites on the same individual (autografts), or between genetically identical twins (isografts), will heal and function normally. In contrast, transplants from members of the same species (allografts) or from different species (xenografts) will be rejected promptly by the host. The phenomenon of acute rejection was defined during World War II by gross and histological examination of skin grafts in humans and in animals. The involvement of immune mechanisms in the process was ascertained by the

observation that a "second set" of grafts from the same donor was rejected at a faster tempo than the first via some type of "memory" intrinsic in the recipient. For the next two decades, however, the most that was known about these events was that increasing numbers of host leukocytes collecting in and around the allografts led inexplicably to their inevitable and irreversible destruction. Circulating lymphocytes were believed to be particularly critical, as evidence mounted that they were important "immunologically competent" components of host reactivity. The continuous recirculation of a substantial lymphocyte population among the blood, lymph, and somatic tissues allowed the cells to contact and respond to any antigenic stimulus in any location in the body.

It also became apparent by differential ablation of "central" lymphoid organs that there were two major classes of lymphocytes normally present in the body. The effects of removal of the thymus gland were first examined in neonatal mice. The majority of animals lost weight, wasted, and died of laboratory infections. Numbers of circulating lymphocytes profoundly decreased and peripheral lymphoid tissues, including spleen and lymph nodes, atrophied. Most significantly, skin allografts healed and grew hair normally in those that survived. Humoral activity was unaffected. As thymectomy of adult mice with already mature lymphoid tissues produces no such effects, it was concluded that the thymus was the central lymphoid organ critical in the early "schooling" of immature lymphocytes from the bone marrow. These cells become the primary mediators of cellular immunity in the body. Unaffected by thymectomy, the population responsible for antibody production was next defined. The bursa of Fabricius, a lymphocyte-rich blind pouch connected to the cloaca of birds, was found to have immunological function. Following its surgical ablation, young chicks but not adult chickens were unable to form antibody against antigens. However, as their cellular immune mechanisms remained intact, they could still reject skin grafts. Subsequent search for a "bursa equivalent" organ in mammals initially implicated the tonsil and appendix but finally settled on diffuse lymphoid aggregations in the gut and bone marrow.

Stimulated by these findings in the 1960s and 1970s, immunology, transplantation biology, and related sciences exploded. Increasing knowledge about cellular and humoral activity unleashed a torrent of investigations. Effector lymphocytes were found to require the influence of other subpopulations before they could attain full function, as illustrated by the phenomenon of "help" given by thymus-derived (T) lymphocytes to bone marrow- or bursa-derived (B) lymphocytes to produce antibody, and the effects of one T-cell subpopulation on the behavior of others via elaboration of specific products. Identification of histocompatibility antigens and definition of their critical role in the presentation of antigen at both the cellular and molecular levels unfolded. The introduction of hybridoma technology led to the creation of monoclonal antibodies that have allowed characterization of the inflammatory/immunological cascade involved in a variety of host defenses. Elaboration of receptor physiology, intracellular machinery, and T-cell interaction with the major histocompatibility complex (MHC) of foreign cells and tissues has opened entire fields in molecular biology, with further unraveling of the intricacies of host immuno-responsiveness.

## ACUTE REJECTION

In overresponsive recipients or those in whom immunosuppression is relatively ineffectual, acute rejection of an organ may be a dramatic and frightening event. After several days of satisfactory function of a kidney transplant, for instance, levels of serum creatinine begin to rise. The patient often develops fevers and malaise. The graft, easily palpable through the lower abdominal wall, may enlarge and become tender. Occasionally, the tense and swollen organ ruptures, with significant bleeding into the retroperitoneal space.

This immunological destruction of an allograft involves a cascade of host-directed, lymphocyte-mediated events. Small numbers of naive lymphocytes become specifically sensitized by antigen-presenting cells in the graft. Some of these stay at the site; others circulate through host peripheral lymphoid tissues where they disseminate the antigenic message and attract newly activated cell populations to the foreign tissues. Progressive infiltration by host mononuclear cells is characteristic of acute rejection of all allogeneic organs. Within a few hours of revascularization, increasing numbers of T and B lymphocytes enter perivascular areas and then invade the graft substance itself over the next days or weeks. The primary responsibility of T cells in the acute destructive process has been emphasized *in vitro* by their ability to lyse donor target cells directly and *in vivo* by the inability of T-cell-depleted animals to reject allografted tissues. Allostimulated B lymphocytes differentiate into antibody-producing immunoblasts and plasma cells in graft and host lymphoid tissues within a few days of transplantation. Although these secrete both antigen-specific and nonspecific antibodies, their precise role in the acute process remains enigmatic. As inflammation proceeds, the increasingly obvious presence of macrophages is associated with progressive

destruction of pericapillary tissues, interstitial inflammation, and eventual tissue necrosis. Macrophages have several roles in graft destruction. They act as antigen-presenting cells to activate lymphocyte populations. They are a principal site of control by MHC immune response genes, mediated particularly by receptors on their plasma membranes for some histocompatibility antigens. They also elaborate cytokines when activated, particularly interleukin 1 (IL-1) and IL-6, which have specific effects on cells of the host and tissues of the graft.

## HISTOCOMPATIBILITY ANTIGENS

Antigens on allogeneic cell surfaces allow the graft recipient to recognize that the transplanted tissue is not "self." It has long been realized that the immune responses between genetically dissimilar humans are directed against a single cluster of alloantigens, designated by the World Health Organization as HLA and encoded by MHC genes found on chromosome 6. There are two MHC antigen groups: class I (HLA-A and B) and class II (HLA-DR, -DQ, and -DP). HLA, -B, and -DR are the most important targets for host alloreactivity. These are expressed on various tissues, may be up- or down-regulated by host cells and their products, and may differentially influence graft rejection. Class I antigens are relatively ubiquitous and are constitutively expressed on all somatic cells. They interact exclusively with the cytotoxic/suppressor $CD8^+$ T-lymphocyte subpopulation. Class II antigens activate selectively the helper/inducer $CD4^+$ T-lymphocyte subpopulation. They are distributed more selectively throughout lymphoid tissues and are present on various antigen-presenting cells, circulating B lymphocytes, and monocytes. Up-regulation of these antigens on the vascular endothelium of transplanted organs by early injury such as ischemia/reperfusion become particularly important as the vascular endothelial cells are exposed continuously to circulating effector cells and their products. Particular leukocyte-derived factors can also stimulate MHC antigens differentially by inducing class II gene products or promoting class I antigens over class II. Interferon-γ (IFN-γ), for instance, up-regulates class II but not class I antigens on several cell types, increasing antigen presentation and amplifying graft immunogenicity.

## ANTIGEN RECOGNITION

Recognition of graft "foreignness" by T lymphocytes requires both MHC molecules and alloantigen. Alloantigen is recognized by the T-cell receptor either "directly" as intact allo-MHC on the surface of donor cells or "indirectly" as processed peptides derived from donor MHC and presented by recipient MHC molecules in their peptide-binding groove on the surface of the antigen-presenting cells (Fig. 1). The recognition of a foreign peptide bound to a MHC molecule is the physiological pathway by which all microbial invaders are recognized and eliminated by T cells. Genetic rearrangements of specific molecules covalently linked by disulfide bonds produce combining sites on lymphocyte surfaces that can recognize virtually any antigen. Acute rejection is thought to be mediated primarily by direct allorecognition, whereas the indirect pathway appears to play a major role in chronic rejection.

Antigen recognition by T cells alone, however, is not sufficient to trigger host events. A two-signal process of lymphocyte activation involves binding of transplantation antigens to T-cell surface receptors (signal 1) coincidentally receiving a co-stimulatory signal 2 from adjacent accessory molecules (Fig. 2). These include a series of receptor–ligand interactions such as CD2–LFA-3 (cluster determinates 2–late functioning adhesion molecule) and LFA-1–intercellular adhesion molecule. Another particularly well-characterized combination is the T-cell surface molecule CD28 that binds to either of its ligands, B7-1 or B7-2, themselves expressed on the surface of bone marrow-derived antigen-presenting cells. The interaction between the T-cell receptor and the MHC alloantigen in the presence of appropriate "co-stimulatory" signals forming a multimolecular patch is recognized as the central event that initiates lymphocyte activation. This triggers further events that lead ultimately to immunological rejection.

## CELL PRODUCTS

With understanding of the cell populations involved in host alloresponsiveness has come appreciation of the critical importance of their products, the cytokines and chemokines (Fig. 3). These molecules may activate or inhibit the function of other cell populations. Antigen-activated macrophages elaborate IL-1, for instance, a monokine that stimulates $CD4^+$ cells to elaborate a series of associated factors, and IL-6, a fibrosis-inducing factor associated with chronic rejection. Other cytokines released by macrophages and important in graft destruction include tumor necrosis factor α (TNFα) and IFN-γ. T-cell- and macrophage-associated chemokines include a series of small molecules such as RANTES (regulated upon activation, normal T-cell expressed and secreted) and monocyte chemotactic protein-1. These are chemoattractants that bring uncommitted macrophages to the site of inflammation.

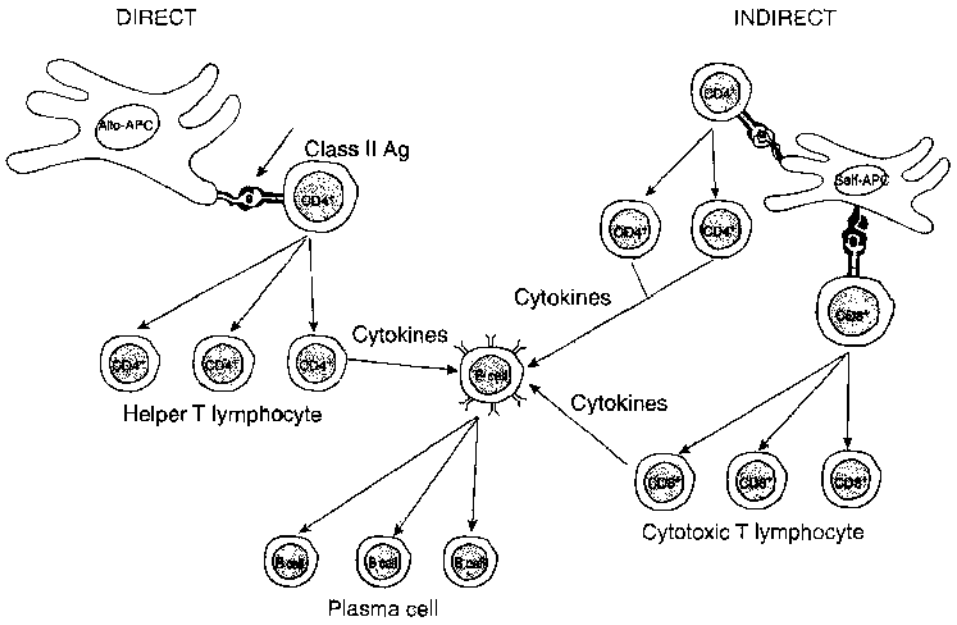


**FIGURE 1** Mechanisms of recognition of alloantigen by the T-cell receptor are shown. "Direct" recognition involves intact allo-MHC on the surface of donor cells. "Indirect" involves processed donor MHC peptides presented in the antigen-binding site of recipient antigen-presenting cells.

T cells can be divided into two subclasses, $T_H1$ and $T_H2$, each of which elaborates distinct cytokines with their own properties and actions. One of the most important, $T_H1$-derived IL-2, stimulates activated T and B lymphocytes to differentiate and proliferate in both an autocrine and a paracrine fashion. Other cytokines encourage B-cell maturation or affect cell populations in the bone marrow. $T_H1$-derived IFN-γ has several effector roles including augmentation of the alloaggressiveness of macrophages previously uncommitted toward the foreign tissue, induction and amplification of MHC antigen expression on graft cells, and stimulation of B cells to increase antibody production. This factor may also increase lymphocyte adhesiveness to an antigen-presenting site by enhancing expression of surface LFA-1. Factors produced by $T_H2$ cells, primarily IL-4 and IL-10, in contrast, are inhibitory proteins to $T_H1$ cells and act to balance or modulate the activity of effector molecules. However, $T_H2$ cells can also increase the expression of B cells and immunoglobulin G production.

Antigen stimulation causes T lymphocytes to upregulate receptor expression on their surfaces that are specific for transferrin, insulin, IL-1, IL-2, and other cell products. The development of high-avidity surface receptors for IL-2 (IL-2R) on most activated $CD4^+$ and $CD8^-$ T lymphocytes, some B cells, dendritic cells, and macrophages, is particularly important in the rejection cascade. Binding of this cytokine to its receptor is followed by internalization of the entire complex,

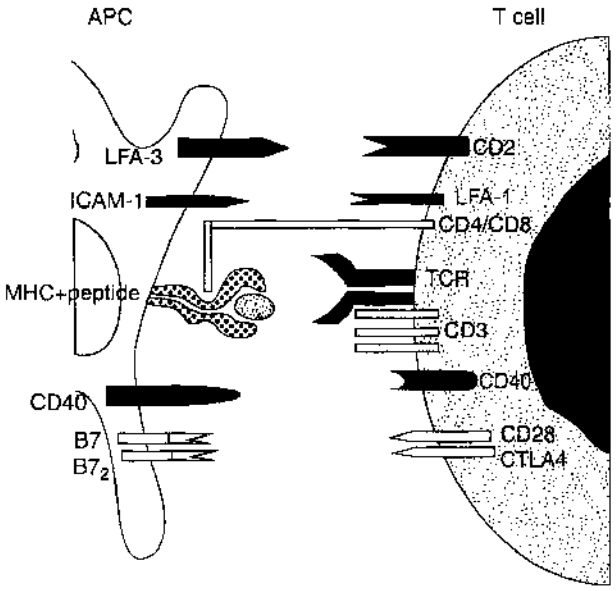


**FIGURE 2** The two-signal process of lymphocyte activation is noted. Signal 1 involves the MHC antigen–T-cell receptor interaction. The co-stimulatory signal 2 includes a series of receptor–ligand interactions.

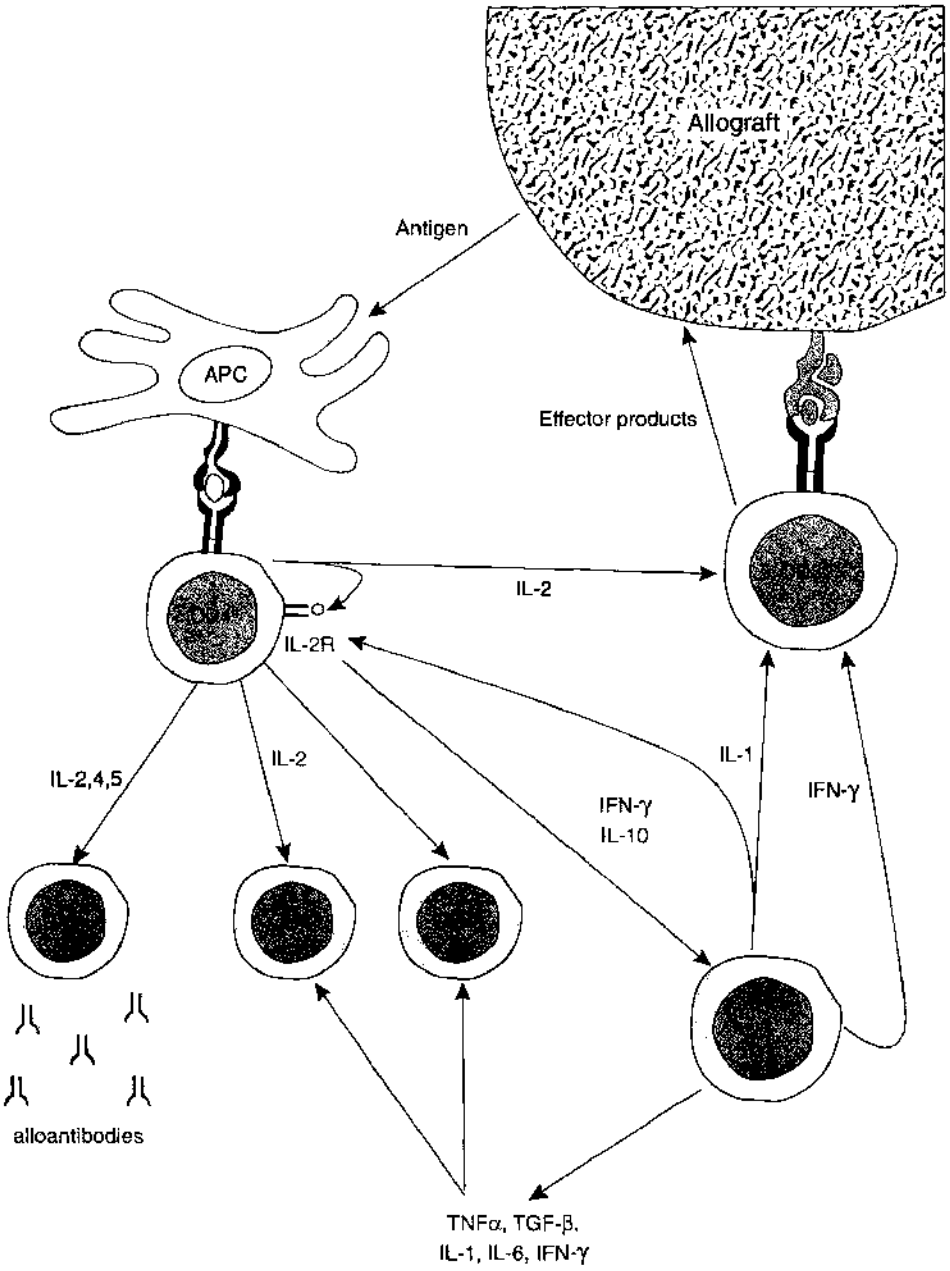


FIGURE 3 Activated lymphocytes and macrophages elaborate a series of cytokines and chemokines that influence the function of other cell populations.

transducing the signal for proliferation and clonal expansion of the antigen-activated cells and driving the entire rejection event forward. This important triggering population is relatively small; only approximately 15% of infiltrating cells in acutely rejecting rat cardiac grafts, for instance, are IL-2 receptor positive. The actual killing of foreign cells may occur via specific T-cell products, particularly granzyme B, a serine esterase protein, and perforin, a pore-forming lytic protein. These plus other effector molecules, in addition to actual cell to cell interactions, produce actual graft destruction.

## CHRONIC REJECTION

The phenomenon of chronic rejection is characterized by gradual functional deterioration of a grafted organ associated with characteristic histopathological changes. Chronic rejection affects all solid organ transplants;

for instance, cadaver kidney transplants have a half-life of less than a decade despite progressive improvements in early results. The clinical manifestations of chronic kidney transplant rejection include the development and worsening of proteinuria and decline in other functional parameters. Morphologically, glomeruli become increasingly sclerotic, tubules become atrophic, and interstitial fibrosis increases progressively. The prognosis for heart and lungs is worse. Graft arteriosclerosis occurring in heart transplants and broncheolitis obliterans developing in lung transplants are characteristic chronic changes in those organs.

Several risk factors have been implicated. Alloantigen-dependent factors include histocompatibility differences between donor and recipient, the occurrence of early acute-rejection episodes, and continuing host alloresponsiveness not fully inhibited by routine immunosuppression. Alloantigen-independent factors include donor brain death, ischemia/reperfusion injury, and donor-associated factors such as age, diabetes, and hypertension. These early injuries or conditions predispose the organ to immunological injury and progressive later dysfunction.

The pathophysiology of the chronic process is multifactorial. A critical feature of the phenomenon, the compromise of vessels or other hollow structures, is conceptualized as stemming from recurrent injury to endothelial cells, leading to their persistent activation. Initial acute damage, regardless of etiology, may lead to up-regulation of adhesion molecules, antibody, and antigen–antibody complexes. A sequential pattern of adhesion molecule and cytokine expression has been associated experimentally with macrophage infiltration. This population may release cell mediators including endothelin, a potent vasopressor agent, and IL-1, IL-6, TNFα and transforming growth factor-β, all of which are fibrosis-inducing cytokines. Growth factors and other pro-inflammatory mediators increase the deposition of mesangial matrix. The resultant intimal proliferation, hypertrophy, and repair produce gradual lumenal obliteration.

The deleterious effect of chronic rejection on graft survival continues to reduce substantially much of the promise that transplantation can offer patients with organ failure.

## Acknowledgments

This work was supported by U. S. Public Health Service Grants 5 RO1 1DK46190–28 and 1 PO1 AI140152–05.

## See Also the Following Articles

**Liver Transplantation • Lymphocytes • Pancreatic Transplantation • Short Bowel Syndrome and Intestinal Transplantation, Pediatric • Small Bowel Transplantation**

## Further Reading

Chertow, G. M., Milford, E. L., Mackenzie, H. S., *et al.* (1997). Antigen-independent determinants of cadaver kidney transplant failure. *J. Am. Med. Assoc.* **276**, 1732.

Häyry, P., von Willebrand, E., Parthenais, N., *et al.* (1984). The inflammatory mechanisms of allograft rejection. *Immunol. Rev.* **77**, 85–142.

Krensky, A. M., Weiss, A., Crabtree, G., *et al.* (1990). T-lymphocyte antigen interactions in transplant rejection. *N. Engl. J. Med.* **322**, 510.

Mason, D. W., and Morris, P. J. (1986). Effector mechanisms in allograft rejection. *Annu. Rev. Immunol.* **4**, 119.

Sayegh, M. H., and Turka, L. A. (1990). The role of T-cell costimulatory activation pathways in transplant rejection. *N. Engl. J. Med.* **338**, 1813.

Springer, T. (1994). Traffic signals for lymphocyte recirculation and leukocyte emigration. *Cell* **76**, 301.

Tilney, N. L., Whitley, W. D., Diamond, J. R., *et al.* (1991). Chronic rejection: An undefined conundrum. *Transplant* **52**, 389–398.

# Trauma, Overview

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**blunt injury** A mechanism of injury that deforms tissue on impact and causes tissue disruption when the elastic forces of the tissue are exceeded.
**hypotension** Low blood pressure.
**multiorgan failure** Malfunction progressing to complete failure of vital organs that occurs after shock and infection in a trauma patient.
**penetrating injuries** Caused primarily by stab wounds and bullets, these injuries are the result of cutting or lacerating tissue.
**peritoneal lavage** A technique to access hemorrhage into the abdominal cavity whereby a small tube is inserted into the space and fluid is instilled into the cavity and then removed to determine whether free blood is present.
**shock** A marked decrease in tissue perfusion usually associated with a fall in blood pressure that deprives vital tissues of oxygen.

**Trauma refers to injuries that cause structural alterations and physiological imbalances in the body. Physical** or chemical agents can damage tissue. In general terms, **trauma refers to accidental injuries, although there are occasions, such as wars or suicide, when trauma is intentionally inflicted on an individual. Moreover, the surgeon who performs elective surgical procedures causes injury** to tissue with the initial skin incision, yet the circumstances are such that the skin is free of bacteria, the scalpel is sharp, and blood loss is controlled, thus minimizing tissue injury and its subsequent effects. In contrast, accidental injury disrupts tissues and is associated with bacterial contamination and uncontrolled blood loss. The body responds to such tissue disruption by clotting the damaged blood vessels to control the hemorrhage and then initiating an inflammatory response to clear the dead tissue and kill bacteria that have contaminated the wound. Finally, major systemic changes, such as fever, tachycardia, and increased protein breakdown, occur to support this regional inflammatory process and to enhance wound healing.

## SCOPE OF THE PROBLEM

Unintentional deaths due to trauma are a major cause of mortality and disability in the United States, occurring primarily in young active adults and children. In the year 2000, 97,300 individuals died due to accidents; a fatal injury occurred every 5 min and a disabling injury occurred every 1.5 s. The National Safety Council estimates that the cost of these injuries, including lost wages, medical expenses, property damage, employer costs, fire and other loss, was $512.4 billion in 2000, which equaled approximately $5000 for each U.S. household. The leading causes of unintentional-injury deaths in the United States are shown in Table I.

The major cause of accidental injuries in the United States is motor vehicle crashes. There is a death every 12 min and a disabling injury every 14 s due to automobile accidents. The age group most affected ranges from 15 to 24 years but the very old (>75 years) are also greatly affected. Motor vehicle accidents are now the major cause of death for teenagers. More than one-third of the accidents involved an intoxicated or alcohol-impaired driver or nonmotorist. The increased use of recreational drugs also contributes to this high vehicle-related accident rate.

There were over 5000 deaths in the workplace due to unintentional injuries and almost 4 million workers suffered disabling accidents. This accounts for a cost to Americans of $131.2 billion, which exceeds the combined profits of the top 13 companies in the Fortune 500.

Approximately 30,000 fatalities and over 7,000,000 disabling injuries occurred in the home. There is a fatal injury every 18 min in the home and a disabling injury every 4 s. The leading causes of these fatal events are poisonings, falls, fires and burns, and suffocation.

There were approximately 22,000 fatalities in the community caused by falls, drowning, and transportation accidents. More than one-half of the 750 deaths

TABLE I Leading Causes of Unintentional-Injury Deaths in the United States, 1998

| | |
|---|---|
| Motor vehicle accidents | 43,501 |
| Falls | 16,274 |
| Poisoning | 10,253 |
| Drowning | 4,406 |
| Choking | 3,515 |

 

resulting from boating accidents could have been prevented if the victim had been wearing a life jacket.

## MECHANISMS AND PATTERNS OF INJURY

There are two main types of mechanical injury: blunt and penetrating. The mechanisms and the patterns of injury that are sustained by the body are unique to the type of injury and determine in large part the treatment and outcome.

Blunt injury occurs in automobile accidents, falls, or assaults with blunt objects. The injury caused is a deforming injury related to the force at impact that alters tissue shape by compression. With such force, body tissues stretch and when this elastic capacity is exceeded there is tissue disruption. Blunt injuries damage the skin (abrasions, contusions, and lacerations), cause bone fractures, and result in visceral or vascular rupture. The specific body part injured depends on the magnitude of the force, but also the fixation of the specific tissue and its strength. For example, bones such as the first two ribs, scapula, pelvis, or femur are extremely durable and these areas are fractured only when extreme forces are exerted on these specific areas. Internal organs rupture at points of fixation such the falciform ligament of the liver, the ligament of Trietz that holds the small bowel, or the retroperitoneal cecum. Internal injuries also occur because of close proximity of organs to rigid external structures, the best example being the close proximity of the brain to the skull.

The four common injuries observed in unrestrained drivers are fracture of the femur, fracture of the pelvis, injury to the thoracic cage, and fracture of facial bones. The common pattern of injury seen in a pedestrian struck by a motor vehicle is fracture of the upper third of the fibula and tibia. Injuries to the ribs and abdominal viscera occur if the individual is thrown onto the car hood. As the individual falls to the ground, head and facial injuries may occur.

Penetrating injuries are primarily caused by stab wounds and bullets. The energy involved with a stab wound is relatively low and hence these wounds are lethal only if a vital organ, such as the heart, is penetrated. Missile wounds penetrate by cutting or lacerating tissue. In addition, depending on the bullet type and the force exerted, there may be extensive tissue damage due to cavitation. The injury pattern in patients with penetrating injuries is much more random and depends on the location of the penetration and the cause of the injury.

## PREVENTION

Clearly, the success to the reduction of accidental injuries is prevention. Because automobile accidents account for approximately one-half of the deaths due to trauma, there is increasing pressure to utilize preventative measures to reduce vehicle accidents. In fact, deaths from this cause are decreasing. The public health measures contributing to this success include improved design of automobiles and equipment, the mandatory use of restraint devices, reduction in highway speed, and campaigns against individuals who drink and drive.

In the area of penetrating injuries, prevention has a role by controlling gun use and gun availability. This, however, is an extremely controversial issue, but it is quite clear that countries that have gun restrictions have a much lower injury rate related to missiles than the United States.

Prevention plays a major role in injury reduction in the workplace. The high cost of such accidents more than justifies preventative programs and individuals skilled in this area are frequently employed by large companies to participate in program planning and education. Annual reports of accidents are often mandated by governmental agencies.

Accident prevention in the home is more difficult to control and occasionally is related to the manufacture of unsafe products used in the home and the sale of toys that are potentially dangerous. Consumer pressures work to improve product design in this area.

## CONSEQUENCES OF INJURY

### Shock

One of the first problems associated with injury is blood loss or hemorrhage. This may be visible, associated with loss of or damage to skin or a fracture of a long bone that is compounded and protruding through skin and soft tissue. However, much bleeding is internal with loss accumulating into cavities of the chest or thorax or into soft tissue, causing marked swelling.

The volume of blood in an adult represents approximately 7--8% of the body's weight and blood pressure is usually well maintained with losses up to 25% of this amount. However, with additional bleeding, hypotension, e.g., a low blood pressure, occurs.

Shock refers to this situation when blood flow and pressure are inadequate to sufficiently oxygenate essential tissues of the body. As a result, the normal process that produce high-energy compounds, such as ATP, which serve as fuel for cells, is impaired and cell function is depressed. Acid accumulates within the body

and this acidemic environment further limits cardiac, renal, pulmonary, and brain function. The hemorrhage must be controlled and the blood volume restored. The latter is accomplished by starting an intravenous infusion of a salt-containing solution that temporarily expands the blood volume and raises the blood pressure. With ongoing loss of blood, the transfusion of red cells is required, for these are the cells that provided for the oxygen-carrying capacity of blood. The type of shock associated with blood loss is referred to as hypovolemic shock.

There are several other causes of shock in the injured patient. Cardiac contusion or cardiac tamponade may result in a falling blood pressure because the heart has limited ability to pump blood throughout the body. This situation is referred to as cardiogenic shock. There are occasions when an injury to the nervous system occurs and the blood pressure falls. The usual injury is associated with spinal contusion or transection of the cord and these situations result in dilation of blood vessels that have been interrupted from their nervous connections.

## Systemic Injury Responses

Trauma produces a fairly predictable and reproducible set of systemic responses. Initially, injury responses were said to follow an ebb and flow course; that is, metabolic and physiologic processes were generally slowed during the shock period and accelerated with fluid resuscitation and restoration of blood volume. With debridement and repair of the injured site, the body increases its responses, presumably in an effort to accelerate wound healing. The clinical manifestations of this response are fever, tachycardia, and increased ventilation. The body's metabolism is altered and there is increased oxidation of fat and the accelerated breakdown of protein, presumably to provide fuel and amino acids for the healing wound. In short, the patient's own tissue is broken down to ensure tissue repair. With mild to moderate injuries, these catabolic responses cause minimal debility, but with more extensive injuries these responses cause marked weight loss and erosion of muscle tissue. This can be counterbalanced in part by aggressive nutritional support and exercise. With wound healing and/or resolution of the injury, the processes abate and the individual starts to regain weight and strength.

## Infection and Organ Failure

Skin is an important barrier to microorganisms and its integrity is paramount to defense against infection. With trauma to this important barrier, the individual becomes susceptible to invasive infections. This situation is compounded by the fact that many injuries occur in environments where the wounds are contaminated by dirt and other debris. With stabilization of the patient, the wound must be washed and cleaned in order to reduce the bacterial load and achieve a situation where host defenses can handle the number of bacteria that are present. Antibiotics are administered intravenously and tetanus toxoid is also given to enhance antibody production to the organisms that are responsible for this potentially lethal infection. Other infections may be expected, particularly in the abdomen if rupture of an abdominal viscera has occurred. If the patient requires long-term mechanical ventilation, associated pneumonia is also a possibility.

With the occurrence of shock and associated infection, there is a high probability that associated organ failure may occur. This syndrome is manifest as failure of one or more organs including the kidneys, liver, coagulation system, lungs, and central nervous system. The cause of this sequence of organ failure in not known, but it is hypothesized that products of the inflammatory response overwhelm the body and cause organ damage. Sequential organ failure is now the most common cause of late deaths in the patient who sustains traumatic injuries and the only available therapy is supportive care.

## Site-Specific Injuries and Their Consequences

### *Head Injuries*

Injuries to the head are frequent, disabling, and potentially life-threatening because of the delicate nature of the brain. Although emergency measures can be initiated in the field where the injury occurred, careful rapid evacuation of the patient to a hospital's emergency facility is essential for appropriate diagnosis and treatment.

Physicians assess the extent of the patients brain injury using a scoring system based on physical signs and symptoms. This scoring system aids prediction of the mortality and morbidity related to the injury. For example, 10% of individuals with a score of 14–15 will have some chronic disability related to their injury and almost all those with a score of 8 or lower will have disabilities and approximately 30% will die.

Once the patient has stabilized, a computed tomography (CT) scan is indicated, and if necessary, an emergency operation is performed. These procedures aim to control hemorrhage and evacuate blood clots within the brain. In addition, by opening the bones of the skull, the pressure within the cranium is reduced. Because the skull is a closed container, brain swelling

results in increased intracranial pressure, which at some point causes damage to the central nervous system. This pressure is carefully monitored and can be controlled by withdrawing fluid from compartments within the brain or by controlling blood pressure and the amount of intravenous fluid administered to a patient. This type of care is best performed in an intensive care unit, particularly those with individuals trained in neurosurgical care.

### *Extremity Injuries*

These injuries involve damage to the skin and soft tissue, injuries to blood vessels and fractures to the long bones. All of these injuries may occur in the same patient and be apparent in the same extremity, and such situations are extremely challenging to the surgical team. With the development of refined techniques in vascular and peripheral nerve surgery, transected limbs or digits can be reimplanted with a reasonably good chance of rehabilitation.

### *Injuries to the Abdomen*

Injuries to the abdomen vary greatly, depending on the mechanism of injury and the force involved. For example, approximately 30% of stab wounds to the abdomen fail to fully penetrate the subcutaneous adipose tissue and do not enter the abdominal cavity. The initial role of medical providers following abdominal injury is to assess the extent of intra-abdominal hemorrhage. This is accomplished by performing a procedure referred to as peritoneal lavage. This involves placing a small tube in the peritoneal cavity, instilling liquid through the catheter, and then withdrawing the fluid. The sample can then be examined to assess the amount of blood present and a decision can be made as to whether an operation is indicated to control the hemorrhage. An alternate diagnostic approach is to use ultrasound to detect the presence of intra-abdominal fluid. A CT scan is then performed to further localize the site of injury.

Extensive injuries to the abdomen often involve destruction of portions of the liver or the spleen and associated damage to other organs. These traumatic injuries are devastating, for blood loss is massive and tissue damage is extensive and highly lethal. Surgeons often perform several sequential operations in an attempt to salvage these patients. First, the bleeding is stopped and bacterial contamination controlled. Six to 12 h after the initial operation, when the patient has returned to a more normal physiological state, the individual is taken back to the operating room and more permanent repair of the damaged tissue is undertaken. Several additional operations may be necessary before restoration of the damaged organs is satisfactory. This approach is referred to as damage control surgery.

### *Burn Injury*

Fires and explosions cause cutaneous burns, which are one of the most extensive injuries that can be sustained. Burns are graded by their depth; a second-degree burn will regenerate skin, whereas a third-degree injury will require skin grafting. The extent of burn over the body is expressed as a percentage of body surface area. A 60% total body surface burn means that 60% of the entire body surface is injured. Both morbidity and mortality are associated with burn size. However, the injury may be more severe with involvement of the hands, face, and genitalia and the association of inhalation of smoke, which causes injuries to the lungs.

Burn patients are cared for in several sequential phases. First, the individual must be resuscitated with intravenous fluid to replace the fluid that leaks out through the area of burn. After several days when the patient has stabilized, the burned skin can be surgically removed and skin grafts applied to these areas. This is performed by taking very thin sections of skin from uninjured areas. The harvested skin is then placed on the site where the burn occurred. The donor site may be reharvested in approximately 2 weeks, for the surface area regenerates in 7–10 days. In patients with large burns covering 70–90% of their body, this procedure of grafting is quite slow and may require 1–3 months of hospitalization. The final stage is rehabilitation, which is required to aid in ambulation, eating, and other aspects of self-care.

## See Also the Following Articles

**Hemorrhage • Lower Gastrointestinal Bleeding and Severe Hematochezia • Occult Gastrointestinal Bleeding • Upper Gastrointestinal Bleeding • Variceal Bleeding**

## Further Reading

American College of Surgeons Committee on Trauma (1997). "Advanced Trauma Life Support for Doctors," 6th Ed. American College of Surgeons, Chicago.

Block, E. F. J. (1999). Diagnostic modalities in acute trauma. *New Horizons* 7, 10–25.

Feliciano, D. V. (1991). Diagnostic modalities in abdominal trauma: Peritoneal lavage, ultrasonography, computed tomography scanning, and arteriography. *Surg. Clin. North Am.* 71, 241–256.

National Safety Council (2001). "Report on Injuries in America." Available at http://www.nsc.org/library/rept2000.htm.

Velmahos, G. C., Tatevossian, R., and Demetriades, D. (1999). The "seat belt mark" sign: A call for increased vigilance among physicians treating victims of motor vehicle accidents. *Am. J. Surg.* 65, 181–185.

# Traveler's Diarrhea

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**diarrheagenic *Escherichia coli*** A group of *Escherichia coli* strains that cause diarrheal illness. Two strains are important causes of diarrhea in international travelers to tropical and semitropical areas: enterotoxigenic *E. coli* and enteroaggregative *E. coli*.

**rifaximin** An unlicensed and poorly absorbed rifamycin antimicrobial agent with activity against enteric bacterial pathogens and effective in reducing the duration of diarrhea when used therapeutically.

**traveler's diarrhea** Diarrhea that occurs when a person leaves his or her home region, consuming meals at foreign eating establishments away from local medical care.

**When persons leave their home region they may experience diarrhea, with rates depending on the type of food and beverages consumed, the place where they were consumed, and the level of hygiene in the country of origin and in the destination. Most cases of diarrhea that occur in high-risk regions of tropical and semitropical countries are due to bacterial enteropathogens found in food and, to a lesser degree, in beverages. Treatment is directed to fluid and salt replacement, diet to facilitate intestinal repair, drugs to improve symptoms, and antimicrobial therapy to eliminate the causative agent and cure the illness. Vaccines are being developed to prevent infection with the most common pathogen, enterotoxigenic *Escherichia coli*.**

## INTRODUCTION

Diarrhea has historically been important in migrating groups when moving from one region of the world to another. It has played a major role in the outcome of many wars up to the 19th century. It has been known for some time that rates of diarrheal illness were reduced as populations remained in a region of risk, suggesting the occurrence of natural immunity. With the growing importance of international travel for pleasure and business, the occurrence and severity of traveler's diarrhea have become a major public health issue. In the past 20 years, a great deal has been learned about the incidence, sources, prevention, and therapy of this illness. A commonly used definition of traveler's diarrhea is the passage of three or more unformed stools per day, together with one or more additional symptoms or signs of enteric infection including nausea, vomiting, fever, abdominal pain or cramps, tenesmus, or fecal urgency, after leaving a home region to travel to a distant location. Illness that occurs shortly after returning home from a trip qualifies when the expected incubation period of enteric infections of 1 to 7 days is considered.

## INCIDENCE

Each year more than 600 million persons cross international boundaries. Of these, more than 50 million travelers venture into tropical and semitropical regions with reduced hygiene levels and put themselves at risk for the development of diarrhea. The world can be divided into three regions based on the risk of acquiring illness by international visitors. Low-risk areas include the United States, Canada, northwestern Europe, Japan, Australia, and New Zealand, with diarrhea in international travelers visiting low-risk regions occurring at a rate of 2–4%. The high-risk areas include Latin America, southern Asia, and most parts of Africa. The risk of diarrhea when visiting these areas from a low-risk country is approximately 40%. There are areas within these high-risk regions where the rate of illness is lower among travelers than would be expected, such as Costa Rica and southern Africa. Countries in the northern Mediterranean, Caribbean countries, Russia, and China represent the third category of intermediate-risk regions where illness rates for diarrhea among international visitors range from 10 to 20%. Again, a homogenous risk is not seen for travelers to these regions. Within the Caribbean, rates are higher on certain islands (e.g., Jamaica) than others (British and U. S. Virgin Islands). The background rate of traveler's diarrhea of 2–4%, which is seen in all travelers, may relate to the frequency of meals eaten out of the home and possibly to psychic stress and increased alcohol consumption seen in many travelers. This 2–4% rate of illness is also seen among persons from high-risk regions traveling to low-risk countries (e.g., Mexicans traveling to the United States).

 

## RESERVOIRS AND ETIOLOGY

In high-risk and moderate-risk areas, food- and public-hygiene standards are low, explaining the common exposure to diarrhea-producing microbes. The major source of enteric infection in high-risk urban areas is contaminated food. Growing crops in pathogen-enriched soil, failure to wash food items after harvesting, improper handling and cross-contamination within kitchens, and keeping foods at room temperature between meal services all contribute to widespread microbial contamination of food. Beverages may become contaminated because of inadequate water treatment and by groundwater contamination of water supplies during periods of heavy rainfall.

The major pathogens of traveler's diarrhea are bacterial pathogens, which explain up to 80% of illness. The most important bacterial pathogens occurring worldwide among international travelers are enterotoxigenic *Escherichia coli* (ETEC) and enteroaggregative *E. coli* (EAEC), together explaining approximately half of the illnesses seen. ETEC produces a secretory diarrhea as a result of elaboration of toxins and EAEC produces diarrhea secondary to an inflammatory, cytokine-mediated process. Other bacterial pathogens include *Campylobacter jejuni*, which is particularly important in travelers to Asia, *Shigella* spp., *Salmonella* spp., *Aeromonas hydrophila*, *Plesiomonas shigelloides*, and noncholera *Vibrio* spp. Viruses, including rotavirus and Norwalk-like calciviruses, explain approximately 10% of illness of travelers, and parasitic agents (*Giardia* spp., *Cryptosporidium* spp., *Cyclospora cayetanensis*, *Microsporidium* spp., and *Entamoeba histolytica*) are responsible for approximately 2% of illness in international visitors to high-risk areas. Parasitic pathogens are important in certain regions of the world. *Giardia* and *Cryptosporidium* are commonly seen in travelers to Russia (particularly St. Petersburg). *Giardia* and *Cyclospora* are commonly found in travelers to Nepal.

## CLINICAL FEATURES

Most patients with traveler's diarrhea (~75%) experience the passage of watery stools, without significant fever, with untreated illness lasting between 5 and 7 days. Abdominal cramps and pain can be disabling. All the enteric pathogens mentioned above may produce this syndrome. In approximately 3% of travelers with diarrhea, febrile dysentery (passage of bloody stools) is the clinical expression of illness and in these cases, strains of *Shigella*, *Campylobacter*, *Salmonella*, noncholera *Vibrio*, and *Aeromonas* may be responsible. In approximately 10% of cases, vomiting is the major clinical expression of the illness where viruses (Norwalk-like calciviruses or rotaviruses) or preformed toxins of *Staphylococcus* or *Bacillus cereus* may explain the illness. One-fifth of patients with traveler's diarrhea will be confined to bed, incapacitated with their illness.

In approximately 2% of travelers with diarrhea, symptoms will persist for longer than 1 month, with a good percentage of these persons remaining ill for 6 months or longer. These patients with persistent and chronic diarrhea may develop an illness compatible with irritable bowel syndrome or Brainerd diarrhea and, in a small percentage, inflammatory bowel syndrome might be precipitated or unmasked. *C. jejuni* has been identified as one cause of chronic diarrhea in travelers, with symptoms resembling those of irritable bowel syndrome.

## PREVENTION

### Food and Beverage Selection

It may be possible to reduce rates of diarrhea by selection of safer items to eat and drink. Food and beverage contamination by microbes is reduced or eliminated by heating the item to 59°C. Practically, this is seen for foods that are too hot to touch (steaming hot foods, coffee, tea, and soup). It is a mistake to assume that cooked foods are safe. Hamburgers, which are invariably cooked, often are unsafe because the cooking has taken place at an earlier time before consumption and recontamination has occurred. Foods that are dry (bread), those that have been peeled (fruits), and items that have high sugar content (syrup and jelly) are generally safe. Bottled drinks can be considered safe, particularly if carbonated.

### Chemoprophylaxis

Bismuth subsalicylate can be taken to prevent traveler's diarrhea. Taking two tablets with meals and at bedtime (eight tablets per day) during periods of risk will prevent 65% of the illness that would otherwise occur. Antimicrobial agents may be more effective, with rates of protection reaching 90%. The quinolones are currently the most used outside of areas where quinolone-resistant *Campylobacter* is common, such as Thailand, where one tablet (400 mg norfloxacin, 500 mg ciprofloxacin, or 500 mg levofloxacin) is taken daily during the period of risk.

### Immunoprophylaxis

Vaccines that would prevent infection with the most important cause of traveler's diarrhea, enterotoxigenic *E. coli*, are being developed. An ETEC

whole-cell-binding subunit of cholera toxin, related to ETEC heat-labile enterotoxin (LT), given as an oral vaccine on two occasions, has been found to be ~80% effective in preventing ETEC diarrhea, provided the strains to which the patient is subsequently exposed produce LT or colonization factor antigens contained in the vaccine. Research groups are working on a multivalent vaccine to prevent traveler's diarrhea, considering the multitude of causative agents involved.

## TREATMENT

### Fluids and Electrolytes

As is the case in all forms of diarrhea, fluid and electrolyte therapy is fundamental to treatment. In most cases, encouraging travelers with diarrhea to take fluids (soft drinks and soups) and salt (saltine crackers and soups) is all that is needed to ensure hydration in these otherwise healthy persons. Special attention to oral rehydration should occur with infants, the elderly, and the infirm when diarrhea occurs during travel.

### Symptomatic Treatment

Drugs that treat symptoms may be used to keep travelers healthy enough to make excursions and to function while out of town. Of this group of agents, loperamide is the most active and will reduce the symptoms of diarrhea by 60%. Newer antisecretory agents, which act more physiologically to reduce the loss of fluids and salt, appear to have a bright future in this area. Calmodulin-inhibiting drugs (e.g., zaldaride), a chloride channel-blocking drug (SP 303), and an enkephalinase inhibitor (racecadotril) have all been shown to reduce the passage of unformed stools in patients with acute diarrhea. They may not be quite as effective as loperamide, reducing diarrhea by only approximately 40%, but their more physiologic effect supports their development and general use.

### Antimicrobial Agents

Since most traveler's diarrhea cases are due to infection by bacterial agents, it is not surprising that antibacterial drugs remain a mainstay of therapy. Resistance to trimethoprim–sulfamethoxazole, ampicillin, and doxycycline is currently high, rendering these agents of limited value. The quinolones are the current treatment of choice for traveler's diarrhea in adults in most regions of the world. The doses are norfloxacin 400 mg bid, ciprofloxacin 500 mg bid, or levofloxacin 500 mg qd, for 1 to 3 days, depending on the clinical response. In Thailand, quinolone-resistant *Campylobacter* is a major pathogen. In this locale and for children with severe traveler's diarrhea, azithromycin is probably the preferred drug. The dose of azithromycin for adults is 500 mg once a day for 1 to 3 days, depending on response. For children, 5–10 mg/kg/day for 1 to 3 days for more severe cases of traveler's diarrhea is suggested. A newly developed treatment for this illness is rifaximin, an unlicensed and poorly absorbed rifamycin derivative, which has been shown to be as effective as ciprofloxacin. The dose of rifaximin recommended is 200 mg tid or 400 mg bid for 3 days. For children 2–6 years of age, rifaximin may be given in an oral suspension at a dose of 100 to 200 mg bid and for those 6–12 years of age the recommended dose is 200 to 400 mg bid.

### See Also the Following Articles

**Anti-Diarrheal Drugs • Bacterial Toxins • *Campylobacter* • Diarrhea • Diarrhea, Infectious • Foodborne Diseases • Food Poisoning • Food Safety • Parasitic Disease, Overview**

### Further Reading

DiCesare, D., DuPont, H. L., Mathewson, J. J., *et al.* (2002). A double-blind, randomized, placebo-controlled study of SP 303 (Provir) in the symptomatic treatment of acute diarrhea among travelers to Jamaica and Mexico. *Am. J. Gastroenterol.* 97, 2585–2588.

DuPont, H. L. (2002). Traveler's diarrhea. *In* "Infections of the Gastrointestinal Tract" (M. J. Blaser, P. D. Smith, J. I. Ravdin, H. B. Greenberg, and R. L. Guerrant, eds.), 2nd Ed., Chap. 19, pp. 253–265. Lippincott Williams & Wilkins, Philadelphia, PA.

DuPont, H. L., and Ericsson, C. D. (1993). Prevention and treatment of traveler's diarrhea. *N. Engl. J. Med.* 328, 1821–1827.

DuPont, H. L., and Steffen, R. (2001). "Textbook of Travel Medicine and Health," 2nd Ed., B. C. Decker, Hamilton, Ontario, Canada.

DuPont, H. L., Jiang, Z.-D., Ericsson, C. D., *et al.* (2001). Rifaximin versus ciprofloxacin for the treatment of traveler's diarrhea: A randomized, double-blind clinical trial. *Clin. Infect. Dis.* 33, 1807–1815.

Ericsson, C. D., DuPont, H. L., and Steffen, R. (2003). "Textbook on Travelers' Diarrhea," B. C. Decker, Hamilton, Ontario, Canada.

Gorbach, S. L., and Edelman, R. (eds.) (1986). Travelers' diarrhea: National Institutes of Health Consensus Development Conference. *Rev. Infect. Dis.* 8, S109–S233.

Kean, B. H. (1963). The diarrhea of travelers to Mexico: Summary of five-year study. *Ann. Intern. Med.* 59, 605–614.

Steffen, R., van der Linde, F., Gyr, K., and Schar, M. (1983). Epidemiology of diarrhea of travelers. *J. Am. Med. Assoc.* 249, 1176–1180.

# Trematodes

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**cercaria** Juvenile trematode stage that is shed from an infected snail.
**definitive host** Species in which the adult parasite develops and produces eggs.
**digenean** Having two hosts.
**metacercaria** Encysted trematode stage; life cycle continues following consumption by definitive host.
**miracidium** Ciliated larval trematode stage that is released from the egg.
**monogenean** Having one host.
**operculum** Hinged portion of a trematode egg through which the larva hatches.

**Parasitic trematodes (flukes) consist of monogenean and digenean orders, which require one or more intermediate hosts, respectively, to complete their life cycle. Only the digenean parasites are of medical importance to humans. The major parasitic trematodes of humans include blood-borne, intestinal, and tissue-dwelling forms. Gastrointestinal symptoms, including abdominal pain, diarrhea, and vomiting, may be accompanied by systemic symptoms.**

## TREMATODE LIFE CYCLE AND BIOLOGY

The digenean (two-host) life cycle of a parasitic trematode typically consists of a vertebrate primary host, in which sexual reproduction of the parasite occurs, and an intermediate host, typically an aquatic snail, in which the parasite reproduces asexually. This asexual reproduction produces cercariae, which are motile forms of the worm. After being shed by the intermediate host, cercariae infect the definitive host by percutaneous penetration, or encyst on aquatic plants until consumption by the vertebrate host allows further development. The trematode life cycle is completed when eggs shed by adult worms are excreted in host feces and hatch to release ciliated miracidia, which then infect a suitable intermediate host.

Structurally, trematodes are flat and elongated worms whose outer surface (tegument) contains microvilli that both protect the worm and act as a nutrient absorptive surface. Adult worms possess anterior and ventral suckers, which are useful in maintaining attachment to host tissue. Trematodes posses a blind intestine that originates from the anterior sucker and provides additional absorptive capacity. Insoluble intestinal contents are regurgitated through the apical sucker, whereas liquid waste may be expelled through specialized excretory cells (flame cells).

Diagnosis of trematode infection is commonly accomplished by identification of eggs in feces or urine. The eggs of most species are structurally distinct and the diagnosis can be made by standard light microscopy. With the exception of fascioliasis, the drug of choice for trematode infections is praziquantel.

## BLOOD TREMATODES (SCHISTOSOMES)

Schistosomes are major parasites of humans; an estimated 200–300 million people worldwide are currently infected. The predominant species of *Schistosoma* that infect humans include *Schistosoma mansoni*, found in South America, Africa, and Caribbean islands; *Schistosoma japonicum*, which occurs in Southeast Asia and Japan; and *Schistosoma haematobium*, found in Africa, India, and the Middle East. Infection occurs when tailed cercariae, aquatic motile forms of the parasite shed from an infected snail, contact and penetrate the skin of a suitable mammalian host. After shedding their tail, the cercariae transform into the first parasitic stage, the schistosomula. The schistosomula enter the bloodstream and migrate via the circulatory system through the heart and lungs, ultimately reaching the mesenteric veins (*S. mansoni* and *S. japonicum*) or the veins draining the bladder (*S. haematobium*). The males and females mate, producing eggs that are released into the bloodstream and the intestine or bladder, depending on the infecting species.

Acute schistosome infection may be associated with a variety of systemic symptoms, including fever, chills, cough, abdominal pain, vomiting, and urticaria. These symptoms generally occur 4–8 weeks after infection, and coincide with the emergence of antischistosomal antibodies. When associated with *S. japonicum* infection, this acute syndrome is referred to as Katayama

 

fever. Chronic schistosomiasis results primarily from the host immune response directed against parasite eggs. The eggs of *S. mansoni* and *S. japonicum* are shed into the mesenteric venules; some of the eggs migrate to the small intestine, where they may cause severe intestinal irritation. Many eggs are carried by the mesenteric circulation to the liver, where they elicit an intense, immunoglobulin E (IgE)-mediated inflammatory response. Chronic intrahepatic inflammation leads to granuloma formation and ultimately scarring and fibrosis. These changes eventually cause cirrhosis of the liver, with portal hypertension, ascites, formation of varices, and splenomegaly. Evidence also suggests that the risk of hepatocellular carcinoma is increased with chronic schistosomiasis. Because *S. haematobium*, unlike *S. mansoni* and *S. japonicum*, resides within the venous plexus surrounding the urinary bladder, eggs accumulate in bladder tissue and are excreted in the urine. Pain and hematuria are common symptoms of infection with *S. haematobium*, with chronic infection associated with an increased risk of squamous cell carcinoma of the bladder.

The diagnosis of schistosomiasis is made by identifying parasite eggs in the stool (*S. mansoni*, *S. japonicum*) or urine (*S. haematobium*) (Fig. 1). Because egg excretion may be sporadic, concentrating techniques may be required. Serologic testing is available through the United States Centers for Disease Control and Prevention, although the tests are not routinely utilized in clinical practice.

The treatment of *S. mansoni* and *S. haematobium* infection is praziquantel (40 mg/kg orally in two divided doses); *S. japonicum* infection is also resolved with praziquantel (60 mg/kg in three divided doses).

## INTESTINAL TREMATODES (*FASCIOLOPSIS BUSKI*, *HETEROPHYES HETEROPHYES*, AND *METAGONIMUS YOKOGAWAI*)

The life cycle of *Fasciolopsis buski* requires a single snail intermediate host, which becomes infected when eggs excreted in the feces of an infected human hatch to release a miracidium. After developing in the snail, cercariae are released and encyst on water plants. These metacercaria are consumed by the definitive host; the released larvae then migrate to the host intestine and develop into adults. Adult worms in the intestine digest mucosal epithelial cells, which leads to inflammation and microabscess formation. The symptoms of infection with *F. buski* include abdominal or epigastric pain, nausea, diarrhea, and vomiting. Heavy infection may be associated with intestinal obstruction or protein-losing enteropathy. The diagnosis is made by identifying the characteristically large eggs, which measure approximately 130 by 80 μm in size, in the feces of an infected individual. Treatment is praziquantel (75 mg/kg), given in three divided doses for 1 day.

Infection with *Heterophyes heterophyes* and *Metagonimus yokogawai* occurs after ingesting undercooked fish containing metacercariae. The immature adults then migrate to the host small intestine, where they mate and attach to the intestinal mucosa. Eggs excreted in the feces hatch to release miracidia, which then infect an intermediate snail host. The snail sheds the cercariae, which infect a second intermediate host, usually a freshwater fish. Symptoms in the human host are usually mild, although heavily infected individuals

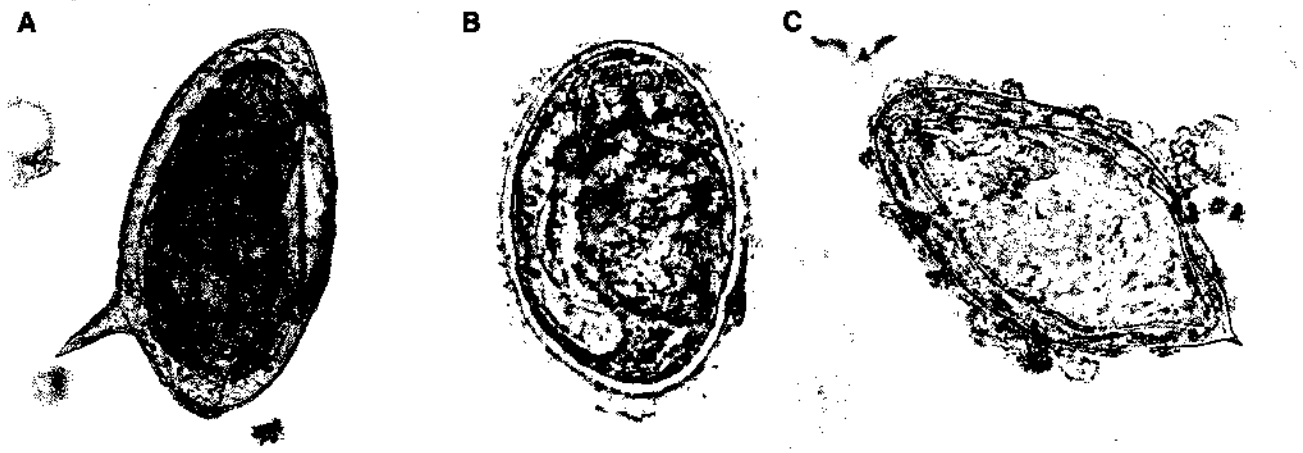


**FIGURE 1** Eggs from the three major schistosome species that infect humans. *Schistosoma mansoni* (A), *Schistosoma japonicum* (B), and *Schistosoma haematobium* (C). Reproduced with permission from Ash and Orihel (1997). Copyright © 1997 by the American Society of Clinical Pathologists.

may experience abdominal pain, nausea, and diarrhea. Rarely the parasites will elicit an intestinal inflammatory response at the mucosal surface that may lead to granuloma formation. Treatment of *Heterophyes* and *Metagonimus* infections is praziquantel, 75 mg/kg administered orally in three divided doses for 1 day.

## TISSUE TREMATODES (*FASCIOLA* SPP., *CLONORCHIS SINENSIS*, AND *PARAGONIMUS WESTERMANI*)

Two species of *Fasciola* cause zoonotic disease in humans. *Fasciola hepatica* (sheep liver fluke) is found in more temperate climates, including Europe, the Americas, and the Middle East, whereas *Fasciola gigantica* (cattle liver fluke) is localized to tropical regions of Asia and Africa. Adult worms, which reside in the bile ducts, release eggs that migrate to the intestine and are excreted in feces. After hatching in fresh water, the miracidia invade a snail intermediate host, in which they multiply and eventually are shed as cercariae. The cercariae attach to aquatic vegetation, and when ingested by a mammalian host, excyst and migrate to the bile ducts. Adults mate for years, and the females release eggs into the biliary tree to complete the life cycle.

Acute infection is characterized by a vigorous host immune response directed at tissue-migrating parasites, and may be associated with fever, abdominal pain, weight loss, and night sweats. Chronic infection is often asymptomatic, but may be associated with signs of biliary obstruction, including jaundice, abdominal pain, and fatty food intolerance. The diagnosis should be considered in individuals with eosinophilia and evidence of biliary obstruction or chronic liver disease. Unfortunately, fecal egg excretion is not present during the acute stage of infection and may be sporadic in chronically infected individuals. Immunodiagnostic tests have been developed, but are not routinely available. The treatment of fascioliasis is bithionol, given orally at a dose of 10 mg/kg for 10 days.

Infection with the liver fluke *Clonorchis sinensis* occurs primarily in countries of Asia, including Japan, Korea, China, Hong Kong, Taiwan, and Vietnam. Adult worms, measuring 10–20 mm in length and 3–4 mm wide, reside in the bile duct of humans. Two intermediate hosts are required for completion of the life cycle. Snails are infected with miracidia that hatch from eggs excreted in human feces. The cercariae are shed from the snail host and infect a cyprinoid fish, which, when ingested by humans, releases the encysted cercariae (metacercaria). Eating raw or undercooked fish is, therefore, the major risk factor for acquiring clonorchiasis. The larvae migrate from the small intestine to the bile duct, where they develop into adults. Within 3–4 weeks following infection, eggs appear in the feces. Symptoms occur as a direct result of the attachment of the worms to the bile duct and the host response to worm antigens. Chronic inflammation of the bile duct may lead to fibrosis and occasionally cirrhosis, as well as to secondary cholangitis, obstructive jaundice, and pancreatitis. In endemic areas, there appears to be an association between clonorchiasis and early-onset adenocarcinoma of the gallbladder. The diagnosis is made by identifying characteristic eggs in the feces of an infected individual. Eosinophilia, leukocytosis, and hyperbilirubinemia are suggestive but nonspecific laboratory findings. Treatment consists of praziquantel, 75 mg/kg divided in three doses for 1 day.

The related fluke *Paragonimus westermani*, like *C. sinensis*, requires two intermediate hosts to complete its life cycle. The first host is a snail, which is infected with the miracidium stage released from eggs in the feces of the primary host. The miracidia enter the second intermediate host, usually a crab, and develop into metacercariae. Humans become infected with the parasite by consuming undercooked crabmeat. The worms hatch in the small intestine, invade the mucosal epithelium, and eventually migrate to the peritoneal cavity. The parasites then traverse the diaphragm, where they reach the lungs and produce eggs. The eggs enter the airways and are coughed up, swallowed, and eventually excreted in feces. Adult worms in the pleural cavity may elicit an intense inflammatory response that triggers abscess formation and fibrosis. Symptoms of paragonimiasis include pleuritic chest pain and cough productive of reddish-brown sputum. Hemoptysis is rare and may signal rupture of a pulmonary blood vessel. Occasionally, adult worms may be found in the heart, mediastinum, peritoneal cavity, and even the central nervous system. The diagnosis is confirmed by identifying adult worms in tissue specimens, or eggs in sputum. Eosinophilia may be present, although this is a nonspecific laboratory finding. The treatment of paragonimiasis is praziquantel, 75 mg/kg divided in three doses for 1 day.

### See Also the Following Articles

**Cestodes • Helminth Infections • Nematodes • Parasitic Diseases, Overview**

### Further Reading

Ash, L., and Orihel, T. (1997). "Atlas of Human Parasitology." 4th Ed. ACSP Press, Chicago.

Haswell-Elkins, M. R. and Elkins, D. B. (1996). Food-borne trematodes. *In* "Manson's Tropical Diseases" (G. C. Cook, ed.), 20th Ed., pp. 1457–1477. W. B. Saunders, London.

Madacsy, L., Molnar, T., Nagy, I., Tiszlavicz, L., and Lonovics, J. (2003). Recurrent nonvariceal upper gastrointestinal bleeding in a patient with gastroduodenal schistosomiasis. *Endoscopy* 35, 230–233.

Ross, A. G., Bartley, P. B., Sleigh, A. C., Olds, G. R., Li, Y., Williams, G. M., and McManus, D. P. (2002). Schistosomiasis. *N. Engl. J. Med.* 346, 1212–1220.

Watanapa, P., and Watanapa, W. B. (2002). Liver fluke-associated cholangiocarcinoma. *Br. J. Surg.* 89, 962–970.

# *Trichinella*

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**cytokines** Proteins produced by T cells and other immune cells; transmit signals that are important for communication among the cells of the immune system and between the cells of the immune system and other cells.

**T helper 1 (Th1) cells** Produce proinflammatory cytokines such as interferon γ and interleukin-2, which are important in macrophage activation as well as in inflammatory and autoimmune reactions.

**T helper 2 (Th2) cells** Produce interleukins (IL-4, IL-5, IL-9, IL-10, and IL-13) that are involved in controlling humoral and allergic immune responses.

***Trichinella spiralis* is a nematode parasite that infects humans and a broad range of mammalian carnivores and omnivores. The resulting disease, trichinellosis, is transmitted through the ingestion of infected meat. Most humans acquire infection by eating infected pork. Experimental infections in mice, rats, guinea pigs, rabbits, and dogs have revealed that all stages of the *T. spiralis* life cycle occur in a single host. The life cycle involves an initial intestinal phase, lasting for about 3 to 4 weeks, followed by a muscle phase in which the parasite encysts and remains in the host for life. The extensiveness of its host range, its ease of maintenance in the laboratory, and its capacity to induce a consistent and multifaceted inflammatory response make *T. spiralis* a unique model for studying the interface between the immune and physiological systems of the gastrointestinal tract.**

## LIFE CYCLE

The life cycle of *Trichinella spiralis* has five stages, of which the first four are larval and the fifth is the adult. Transformation of one stage to another involves molting by the worm. Infection is initiated when a host ingests the flesh of an animal that contains the first-stage larva. Muscle tissue of the ingested flesh and the surrounding cyst walls of the larvae are digested in the host stomach, releasing the larval form. On passage from the stomach to the intestine, larvae immediately invade enterocytes, where they develop into adult male and female worms within 30 hours. The bisexual worms then copulate and 3–4 days later the female worms deposit, ovoviviparously, $F_2$ generation larvae in the intestinal mucosa. These "newborn" larvae access the lymphatics and, through hematogenous spread, reach the capillaries of skeletal muscle, invade skeletal muscle fibers, and become encapsulated, or "encysted." The intestinal phase of trichinellosis lasts about 3–4 weeks, and the muscle phase lasts for the life of the host. Within the host, the intestinal worm population is relatively stable during early infection and is gradually depleted as the host develops immunity. Encysted muscle larvae are not eliminated by the host immune response, but may eventually become calcified.

## PATHOGENESIS OF INFECTION

Signs or symptoms of disease, such as diarrhea, anorexia, peripheral blood changes, and muscle pain, are associated with physiological malfunctions and closely track inflammatory changes caused by the parasite. Inflammation may be induced by nonspecific stimuli due to traumatic damage to tissues or may be mediated through specific immunological reactions involving specific cell types and neural pathways linked

through cytokine intermediaries. Mast cell, eosinophil, and goblet cell hyperplasia characterize the mucosal tissues in infected hosts and are accompanied by physiological changes in digestion, absorption, secretion, and motility. These changes usually diminish when the inflammation subsides and the worms are eliminated.

## INFLAMMATION, PATHOLOGY, AND INTESTINAL IMMUNITY

Immunity can be demonstrated by reinfecting a host that has been previously infected or has been "vaccinated"; vaccination is accomplished by enteral or parenteral injection with antigens from somatic tissues of *T. spiralis* or from excretions or secretions of the nematode. Immunity is evident in that fewer worms from the challenge infection are able to infect the host, and those that do are eliminated at a much faster rate, compared with a primary infection. Various serological or biochemical correlates are also used to measure the immune response.

## IMMUNOLOGICAL REACTIONS AND THEIR INTERPLAY

Infection produces an inflammatory response in the gastrointestinal tract and consists of innate and adaptive immune responses. The innate response involves infiltration of the tissue by neutrophils and macrophages and is associated with changes in secretion, mucus production, and motility. These changes are mediated by cytokines such as interleukin-1 (IL-1). A specific immune response follows and involves the differentiation of T helper (Th) lymphocytes into subsets that are characterized by specific cytokine profiles; these are referred to as Th1 or Th2 responses. *Trichinella* is a potent stimulus of the Th2 response, which is characterized by the secretion of IL-4, IL-5, IL-9, IL-10, and IL-13. These cytokines in turn influence intestinal physiology and hence the ability of the host to evict the parasite. Thus, *Trichinella* infection serves as a robust model in which not only to study the modulation of intestinal physiology by the mucosal immune system, but also to place these interactions in a context of host defense.

Subsequent exposure of the host to *Trichinella* results in rapid expulsion of the parasite due to the acquisition of natural immunity. This is an antibody-mediated type I hypersensitivity response. Cytokines from Th2 cells stimulate B lymphocyte growth, the production of immunoglobulin E (IgE), and the activation of mast cells. Mast cells that become armed with IgE on their surface degranulate when reexposed to parasite-specific antigens. In the process, 5-hydroxytryptamine (5-HT), histamine, and prostaglandin are released from mast cells and act directly on epithelial cells and stimulate secretion of chloride ions and water. Histamine and 5-HT stimulate epithelial cell secretion through another pathway by acting indirectly through enteric cholinergic nerves that regulate chloride secretion. Additionally, mast cell-derived 5-HT and histamine act on intestinal smooth muscle to cause contraction.

The complexity of the mucosal immune response has captured the interest of gastroenterological researchers and has generated insights into human disease states as well as into new treatment strategies. The critical role of the Th2 response in host defense has generated new knowledge regarding the ability of Th cytokines to modulate secretion, mucus production, and gut motility. This has led to an understanding of how diseases characterized by immune activation, such as inflammatory bowel disease (IBD), disrupt intestinal physiology to generate symptoms such as diarrhea and pain. Studies using the *T. spiralis* model in certain mouse strains have prompted the notion that transient infection and immune activation may lead to physiological disruption that persists long after infection and inflammation are resolved. This has provided insights into a common chronic human condition known as irritable bowel syndrome (IBS), which may develop following acute infective gastroenteritis. Finally, the robust nature of the Th2 response during *T. spiralis* infection has provided a model to test the concept of immunological distraction. Prior exposure of the host to a Th1 stimulus distracts the immune system away from a protective Th2 response, and results in chronic infection. Conversely, prior infection with *T. spiralis* polarizes the immune response toward Th2 and away from the deleterious Th1 response associated with experimental colitis, with consequent amelioration of colonic inflammation. This strategy is now being harnessed to treat human IBD and is an example of the utilization of nematode infection to explore mechanisms and treatment of human disease.

### See Also the Following Articles

**Foodborne Diseases • Food Poisoning • Food Safety • Helminth Infections • Nematodes • Parasitic Diseases, Overview • TH1, TH2 Responses**

### Further Reading

Barbara, G., De Giorgio, R., Deng, Y., Vallance, B., Blennerhassett, P., and Collins, S. M. (2001). Role of immunologic factors and

cyclooxygenase 2 in persistent postinfective enteric muscle dysfunction in mice. *Gastroenterology* 120, 1729–1736.

Barbara, G., Vallance, B. A., and Collins, S. M. (1997). Persistent intestinal neuromuscular dysfunction after acute nematode infection in mice. *Gastroenterology* 113, 1224–1232.

Castro, G. A. (1989). Parasite Infections and Gastrointestinal Motility. *In* "Handbook of Physiology—Gastrointestinal Physiology" (J. D. Wood, ed.), pp. 1133–1152. American Physiological Society, Bethesda.

Castro, G. A. (1991). A Physiological perspective: Physiological adaptations in host-parasite systems. *In* "Parasite–Host Associations—Coexistence or Conflict?" (C. A. Toft., A. Aeschlimann, and L. Bolis, eds.), pp. 356–374. Oxford University Press, New York.

Castro, G. A., and Arntzen, C. J. (1993). Immunophysiology of the gut: A research frontier for integrative studies of the common mucosal immune system. *Am. J. Physiol. (Gastrointest. Liver Physiol.)* 28, G599–G610.

Castro, G. A., and Powell, D. W. (1994). The physiology of the mucosal immune system and immune-mediated responses in the gastrointestinal tract. *In* "Physiology of the Gastrointestinal Trac" (L. R. Johnson, ed.), Vol. 1, pp. 709–750. Raven Press, New York.

Elliott, D. E., Urban, J. F., Jr., Argo, C. K., and Weinstock, J. V. (2000). Does the failure to acquire helminthic parasites predispose to Crohn's disease? *FASEB J.* 14, 1848–1855.

Khan, W. I., Blennerhassett, P. A., Deng, Y., Gauldie, J., Vallance, B. A., and Collins, S. M. (2001). IL-12 gene transfer alters gut physiology and host immunity in nematode-infected mice. *Am. J. Physiol. (Gastointest. Liver Physiol.)* 28., G102–G110.

Khan, W. I., Blennerhassett, P. A., Varghese, A. K., Chowdhury, S. K., Omsted, P., Deng, Y., and Collins, S. M. (2002). Intestinal nematode infection ameliorates experimental colitis in mice. *Infect. Immun.* 70, 5931–5937.

# Tropical Sprue

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**acclimatization** Process of adaptation to a new and different climate, environment, or situation.

**bacterial overgrowth** Abnormal bacterial proliferation; within the small intestinal lumen, this results in mucosal alterations and changes in bile salt metabolism.

**malabsorption** Impaired or incomplete absorption of nutrients by the intestine; can result from any abnormality in the process of digestion and/or absorption of nutrients.

**osmotic diarrhea** High-output diarrhea resulting from ingested, unabsorbed nutrients, which act as osmotic agents, drawing free water into the intestinal lumen.

**sprue** A word anglicized by Patrick Manson in 1880 from the Dutch term *sprouw*, meaning "trush," used in seventeenth century Europe to describe a diarrheal disorder with oral aphthous ulcerations.

**Tropical sprue is a malabsorption syndrome of unknown etiology that occurs in residents of and visitors to certain tropical and subtropical areas. It is characterized by abnormalities in the small bowel structure and function that lead to chronic diarrhea and malabsorption with megaloblastic anemia, for which no specific causes can be identified. Tropical sprue may be the ultimate manifestation of multiple diseases with different etiologies.**

## INTRODUCTION

Descriptions of malabsorptive illnesses in the tropics, or tropical sprue, can be found in ancient medical literature, but little progress has been made in the understanding the exact nature of the disease. Two factors, the typical geographic distribution of sprue within the tropics and, in modern times, the response of patients with tropical sprue to sulfonamides and folic acid, have allowed differentiation of tropical sprue from other similar syndromes previously described as nontropical sprue, such as celiac disease, which can be controlled with a gluten-free diet. However, epidemiologic and etiopathogenetic controversies have limited the establishment of a unanimously accepted definition of tropical sprue, and the syndrome remains an enigmatic and commonly overlooked disorder. The absence of a

universal endemicity in tropical and subtropical regions strongly suggests that the etiologic or predisposing conditions are geographically restricted. Multiple factors seem to play a role in the genesis and persistence of the clinical manifestations. The diagnosis can be assumed when other causes of malabsorption have been excluded.

## ETIOLOGY AND GEOGRAPHIC DISTRIBUTION

The etiology and distribution of tropical sprue still defy coherent explanation. Different theories have been put forward, including climatic and sanitary conditions, infectious agents, local dietary factors, and/or immune responses, which would explain the occurrence of the disease in some cases. However, environmental as well as hypothetical genetic factors have eluded discovery so far, and instead of a single disease, tropical sprue may represent a syndrome caused by different etiologies, each with its own distribution.

### Climatic

Lack of acclimatization was one of the initial explanations for the higher incidence of tropical sprue among Europeans living in tropical colonies. Natives were considered resistant to the disease, and adverse climatic conditions were thought to disturb the metabolic balance of unacclimatized people. Some weather conditions, such as a combination of humidity and heat, seemed to correlate with a seasonal variation of the disease. However, a climatic explanation was eventually rejected because there was enough evidence to suggest that tropical sprue was by no means absent in native populations, but rather was overlooked. Furthermore, the disease is not present in all tropical areas of similar latitude and similar atmospheric conditions, and it has been described in climatically diverse regions.

### Infectious

Tropical sprue has been considered an infectious disease because of the endemic and epidemic presentation, the abrupt onset, similar to episodes of traveler's diarrhea seen in some cases, the isolation of different bacteria in jejunal and stool cultures, and the remarkable response of patients to antibiotic therapy.

Tropical sprue occurs both sporadically and in well-defined epidemics, with a patchy distribution in some regions of Asia and Caribbean Islands and at a much lower frequency in Mexico, Central and South America, and Africa. Attack rates are higher in adults than in children, who are normally more frequently affected by most infective diarrheal diseases. The prevalence of endemic tropical sprue has not been clearly established; it tends to be underestimated but may be declining because of the widespread and early use of antibiotics for acute traveler's diarrhea.

Bacteria, viruses, protozoa, and fungi or yeasts have been considered as possible causative agents, but numerous attempts have failed to identify an agent capable of producing all the features of tropical sprue. Enterotoxigenic coliform bacteria (mainly *Klebsiella pneumoniae*, *Enterobacter cloacae*, and *Escherichia coli*) in jejunal aspirates and greater numbers of coliform bacteria in stool cultures have been found in tropical sprue patients in Puerto Rico and India, but studies done in South Africa have shown no difference in the number of coliform organisms, leading to the suggestion of a different pathophysiology. In visitors to the tropics, the disease may be secondary to an impairment in the expulsion of enterotoxigenic coliform bacteria from the gut after an episode of acute diarrhea. Other observations have prompted the conclusion that one or more protozoan parasites, such as *Cryptosporidium parvum*, *Isospora belli*, *Cyclospora cayetanensis*, or *Blastocystis hominis*, may play a causative role. It is also thought that perhaps a yet unrecognized pathogen causes persistent alimentary tract infection or that different infectious agents specific to geographic areas are involved. It is also possible that all microorganisms could represent secondary infections rather than being the primary cause of tropical sprue, as was found to be the case with a superimposed intestinal mycosis that was originally implicated in the etiology of tropical sprue.

### Nutritional

Nutritional deficiencies and unsaturated fat consumption have been proposed as the primary causes of tropical sprue. The former, however, have been eliminated as causative in light of the frequency of tropical sprue in patients on a good diet and the absence of tropical sprue in tropical areas where the population exists on a marginal diet, as well as the recognition that vitamin deficiency can be a consequence of rather than the cause of malabsorption; however, subclinical folate deficiency, being very common in the tropics, may be a contributory factor.

The disease is more prevalent in areas where food is usually fried with cooking oils rich in unsaturated long-chain fatty acids, mainly oleic and linoleic acids (i.e., from pork lard, sesame seeds, and soybeans), whereas its absence in Africa and the English-speaking

Caribbean Islands may be related to the use of more saturated oils (i.e., coconut and palm oils) and the consumption of food that is usually boiled rather than fried. This difference may be important because linoleic acid exerts an important influence in diminishing intestinal *Lactobacillus acidophilus* and thus producing an increase in coliform bacteria. Moreover, unsaturated oils are thought to be susceptible to oxidative rancidity after prolonged storage and exposure to sunlight and high temperature, and rancid dietary fats may induce changes in intestinal functions.

The seasonal incidence of tropical sprue may be related to increased fat consumption during national holidays and festivals, as occurs in Puerto Rico during Christmas season, or to increased fat oxidation during the hotter summer months, as has been observed in the Philippines. These findings provide some explanation for disease distribution but fail to accommodate other features of the disease, such as epidemics. The current trend toward globalization of diets and foods may eventually modify the role of diet in the development of tropical sprue, especially in expatriates.

### Tropical Malabsorption

Some mild abnormalities in intestinal anatomy and physiology are widely prevalent in children and adults in different parts of the tropics. In this subclinical "tropical enteropathy," T cell activation in the lamina propria, may be involved in mucosal abnormalities; this enteropathy is acquired and is usually reversible when a patient leaves the tropics. Its association with tropical sprue is unknown, but tropical enteropathy and tropical sprue seem to be two unrelated conditions with two different, yet unidentified, etiologies, rather than two extremes of the same disease, responding with differential severity to unidentified environmental factors. Tropical enteropathy may, however, render a patient susceptible, and subsequent exposure to an unknown agent may trigger the development of tropical sprue.

### Genetic

Associations of tropical sprue with human leukocyte antigens (HLA) Aw-19 and Aw-31 in Puerto Rico and B-8 in India have been reported. It is possible that these associations represent potential for development of disease in these populations when they are exposed to different specific but as yet unknown agents. Another possibility is that other genes associated with tropical sprue may be in linkage disequilibrium with different HLA genes in different populations.

## PATHOPHYSIOLOGY

There is not universal agreement on the events involved in the pathophysiology of tropical sprue. However, there have been consistent observations of different factors that may interact and lead to development of the clinical manifestations of tropical sprue.

### Basic Lesion

The initial lesion seems to be an acute or subclinical intestinal infection, possibly differing by geography and/or dietary fat intake but leading to persistent and repetitive enterocyte injury. Nutrient malabsorption, mainly impaired fat and folic acid absorption, is secondary to mucosal involvement and leads to osmotic diarrhea and malnutrition, as well as to other alterations that worsen intestinal structure, function, and recovery. Major pathophysiologic disturbances occur in the small bowel but colonic dysfunction may also be found.

### Impairment of Intestinal Structure and Function

Both mucosal damage and increased luminal fat, possibly via gut hormones such as enteroglucagon or peptide YY, lead to small intestinal stasis, which results in bacterial overgrowth and colonization by enterotoxin-producing coliforms. The enterotoxins cause the mucosal abnormalities seen in tropical sprue and weaken the mucosal resistance to bacterial adhesion. At the same time, there is an inhibition of normal gram-positive flora. Administration of antibiotics breaks this vicious cycle by controlling the abnormal flora.

The unabsorbed intestinal fat, mainly an excess of free unsaturated fatty acids, is thought to cause inhibition of $Na^+$,$K^+$-ATPase and $Mg^{2+}$-ATPase (yielding an increased mucosal pH, which decreases the folate absorption), and inhibition of water and electrolyte intestinal absorption; the latter also results from direct damage to colonocytes by the unknown etiologic factor of tropical sprue. Patients suffer from net fluid excretion instead of the normal net absorption, which adds a secretory component to the diarrhea.

### Micronutrient Deficiencies

Low serum folate levels are one of the most common and important findings of tropical sprue. Vitamin $B_{12}$ deficiency occurs as the damage progresses. Both micronutrients play an important role in tissues with the

fastest cell turnover, namely the small intestine and the bone marrow, which characterizes and perpetuates the main clinical manifestations. Although tropical sprue is characterized by a deficiency of all nutrients, treatment with only folic acid hastens enterocyte recovery and usually secures clinical remission.

### Digestive Abnormalities

Impairment of the proximal gut mucosa may lead to a reduction in meal-stimulated exocrine pancreatic secretions. This hyposecretion is associated with the degree of duodenal atrophy and it seems to be secondary to diminished production and release of pancreatic secretagogue hormones, such as secretin and cholecystokinin. Also, most patients exhibit lactose intolerance due to uniformly reduced levels of disaccharidase activity in the atrophic jejunal mucosa. These anatomic abnormalities result in a worsening of the osmotic diarrhea because of deficient nutrient digestion. Both conditions improve when patients receive the specific treatment for tropical sprue.

## CLINICAL FEATURES

No single clinical manifestation or laboratory abnormality is diagnostic of tropical sprue. The outstanding classical symptom is chronic osmotic diarrhea and the clinical spectrum is related to the duration of the disease and the nutritional background of the individual.

The early phase of the disease is characterized by diarrhea of variable intensity, with pale, fetid, and greasy stools; abdominal distension; prominent bowel sounds; anorexia; and fatigue. Tropical sprue usually begins after years in the tropics, but may appear within a short period of arrival or may occur even months or years after leaving a tropical location. Also, it may develop as an acute attack of watery diarrhea associated with fever and malaise followed by chronic manifestations. This latter development usually occurs during epidemics and/or in foreign individuals living in endemic areas. In general, chronic diarrhea with lactose intolerance, progressive weight loss, and megaloblastic anemia are commonly described. Subsequently, clinical findings of nutritional and vitamin deficiencies become prominent as a consequence of malabsorption and reduced dietary intake secondary to anorexia. It is important to note that glossitis, stomatitis, edema, or other data related to nutritional deficiencies, although common, are not consistently present and predominate in undernourished indigenous populations.

## DIAGNOSIS

Tropical sprue should be suspected in any patient who lives, has lived, or visited the tropics and presents with chronic diarrhea with or without clinical evidence of intestinal malabsorption. The first step in diagnosis is the exclusion of a specific cause of chronic diarrhea and then the assessment of intestinal absorption and morphology. Thus, a complete and specialized workup must be done to exclude other diseases with similar manifestations, including bacterial overgrowth, celiac disease, and, particularly, parasitic infection, which may resemble or coexist with tropical sprue, exacerbating its clinical presentation, mainly in endemic areas.

### Malabsorption Assessment

The malabsorption syndrome can be established with fecal fat quantification, D-xylose, and Schilling tests. Fat malabsorption is not consistently present. Serum beta-carotene may be used as a first-line screening test for fat absorptive capacity. Xylose absorption is almost uniformly decreased, making it a sensitive test, although with low specificity. Malabsorption of vitamin $B_{12}$ and folic acid is present in nearly all cases, rendering serum levels of these nutrients low. Hypoalbuminemia can be secondary to impaired protein absorption, but also to inadequate diet, excessive intestinal loss, and reduced synthesis by the liver.

### Morphological Alterations

The jejunal mucosa seems to be the main target in tropical sprue, but the entire small bowel is affected in advanced stages. The degree of mucosal abnormalities correlates with the severity of the malabsorption. Morphological alterations can be identified radiologically or endoscopically. One of the main values of both types of examination is the exclusion of other specific disorders.

Abnormalities in the barium small bowel follow-through examination tend to be somewhat diffuse and nonspecific. There is a slow transit of the contrast material through the gut, an increase in the caliber of the small intestine, and thickening of the folds. The endoscopic evaluation can reveal scalloping of the valvulae conniventes and a mosaic pattern of the mucosa similar to that seen in patients with celiac disease. It also enables a tissue biopsy, which is necessary to exclude other diseases.

Intestinal specimens tend to exhibit a variable loss of villous pattern, with increased crypt depth and cell hyperplasia, apparently resulting from increased cell production and migration to replenish cell loss.

These features tend to decrease in severe lesions. There are lymphocytic and plasmacytic infiltrates in the lamina propria and increasing plasma cell infiltrates with chronicity. Also, lipid droplets stained with oil red O have been consistently found in a thickened basement membrane subjacent to the intestinal epithelium. This finding sharply contrasts with lipid deposits in other conditions but it is not pathognomonic.

## TREATMENT

The priorities in the initial management of tropical sprue are the restoration of water and electrolyte balance and replacement of nutritional deficiencies, mainly folic acid and vitamin $B_{12}$. Symptomatic treatment with antidiarrheal drugs may be required. Pharmacological doses of folic acid (5 mg, by mouth, one time daily) lead to a great improvement in clinical and hematologic manifestations within 10 days, including diarrhea, even if treatment fails to completely correct gut abnormalities. However, the response to this single treatment depends on the chronicity of the intestinal lesions. On the other hand, short-term antibiotic therapy with tetracycline (250–500 mg, by mouth, four times daily) or succinylsulfathiazole (4 g, by mouth, one time daily) improves intestinal morphology and gastrointestinal symptoms significantly. Controversy exists regarding the role of broad-spectrum antibiotics and the duration of treatment. A therapeutic approach with both folic acid and antibiotics, usually given over a period of 1 to more than 6 months, is recommended. The rate and time of recovery may vary in different populations but a complete and permanent cure is expected, mainly in expatriates leaving the tropics. Recurrence of symptoms years after discontinuing treatment has been reported in some native patients.

If there is uncertainty in the diagnosis of tropical sprue in endemic areas, treatment based on folic acid and antibiotics may be wise because there is a rapid clinical recovery in these cases, and the approach can be used as an empiric trial. The efficacy of broad-spectrum antibiotics, the duration of treatment, and evaluations of long-term followup of patients needs to be assessed. Importantly, identification of a clear etiology would allow a more specific therapeutic approach.

## See Also the Following Articles

**Bacterial Overgrowth • Celiac Disease • Diarrhea • Malabsorption**

## Further Reading


Cook, G. C. (1996). Tropical sprue: Some early investigators favored an infective cause, but was a coccidian protozoan involved? *Gut* 39, 428–429.

Fantry, G. T., Fantry, L. E., and James, S. P. (1999). Chronic infections of the small intestine. *In* "Textbook of Gastroenterology" (T. Yamada, ed.), 3rd Ed., Vol. 2, pp. 1641–1659. Lippincott Williams & Wilkins, Philadelphia.

Farthing, M. J. G. (2002). Tropical malabsorption and tropical diarrhea. *In* "Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, Management" (M. Feldman, L. S. Friedman, and M. H. Sleisenger, eds.), 7th Ed., Vol. 2, pp. 1842–1854. Saunders Elsevier Science, Philadelphia.

Glynn, J. (1986). Tropical sprue—its aetiology and pathogenesis. *J. R. Soc. Med.* 79, 599–606.

Haghighi, P., and Wolf, P. L. (1997). Tropical sprue and sub-clinical enteropathy. A vision for the nineties. *Crit. Rev. Clin. Lab. Sci.* 34, 313–341.

Klipstein, F. A., Holdeman, L. V., Corcino, J. J., and Moore, W. E. C. (1973). Enterotoxigenic intestinal bacteria in tropical sprue. *Ann. Intern. Med.* 79, 632–641.

Menendez-Corrada, R., Nettleship, E., and Santiago-Delpin, E. A. (1986). HLA and tropical sprue. *Lancet* 2, 1183–1185.

Mery, C. M., and Robles-Dúaz, G. (2000). Esprue tropical: ¿Una enfermedad inexistente o inadvertida? *Rev. Invest. Clin.* 52, 377–379.

Morales, M., Galvan, E., Mery, C. M., Castro, G., Uscanga, L. F., and Robles-Diaz, G. (2001). Exocrine pancreatic insufficiency in tropical sprue. *Digestion* 63, 30–34.

Westergaard, H. (1995). Southwestern internal medicine conference: The sprue syndromes. *Am. J. Med. Sci.* 290, 249–262.

# Trypsin

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enterokinase The enzyme present on the brush border of small intestinal enterocytes that cleaves trypsinogen, producing trypsin.
serine proteases Family of proteolytic enzymes with a common mechanism of action involving a serine residue at the active site.
trypsin activation peptide The amino-terminal portion of trypsinogen that is cleaved to release trypsin.
trypsinogen The inactive protein precursor of trypsin normally activated in the intestinal lumen.

**Trypsin is a pancreatic protease that plays a key role in the digestion of nutrients in the small intestine. Its precursor, trypsinogen, constitutes approximately 20% of the protein in pancreatic juice. In humans, there are three forms of pancreatic trypsinogen, each coded for by a unique gene. The two major forms, anionic trypsinogen, also known as trypsinogen-1, and the more abundant cationic trypsinogen, trypsinogen-3, have very similar molecular masses, being approximately 25,000 Da with 89% homology at the amino acid level, but can be differentiated immunologically. The cationic form has more basic lysine residues and a more basic isoelectric point. A third variant, mesotrypsinogen or trypsinogen-2, is less abundant and has an intermediate isoelectric point. All three forms can be separated by two-dimensional gel electrophoresis. In the rat, four forms of trypsinogen have been identified at the protein level, with the anionic and cationic forms being most abundant. Although trypsinogen was originally thought to be expressed only in the pancreas, recently two variants have been identified in ovarian and colon cancer. A trypsin-like protein has also been identified in sperm.**

## SYNTHESIS AND ACTIVATION OF TRYPSIN

All trypsins are synthesized as an inactive precursor, trypsinogen, presumably as a protective mechanism to prevent premature activity in the pancreas, which could lead to the inflammatory disease pancreatitis. As with other pancreatic digestive enzymes, trypsinogens are processed through the Golgi apparatus and packaged into zymogen granules to await secretion by exocytosis. This packaging can also be considered a protective mechanism. Trypsin is produced by cleavage of an N-terminal peptide, Ala-Pro-Phe-Asp-Asp-Asp-Asp-Lys, and the tetra-aspartyl group is present in trypsinogens of most species. This peptide, known as the trypsin activation peptide, can also be assayed and used as a measure of trypsinogen activation. Cleavage of trypsinogen can be brought about by trypsin itself at a low rate and much more efficiently by the intestinal protease, enterokinase, a large protein present on the lumenal surface of cells lining the upper intestine. This activation occurs in the intestinal lumen and begins an activation cascade that then activates all the other pancreatic proteolytic enzymes and much of the lipase activity, the latter through activation of colipase (Fig. 1). Enterokinase activity is enhanced by low levels of calcium and bile salts. Trypsin is far more efficient at activating the other enzymes than it is at activating itself. Moreover, the pancreas also synthesizes small amounts of a pancreatic secretory trypsin inhibitor (PSTI), which is packaged with trypsinogen in zymogen granules and is capable of inhibiting small amounts of active trypsin. Trypsinogen can also be activated by certain cathepsins,

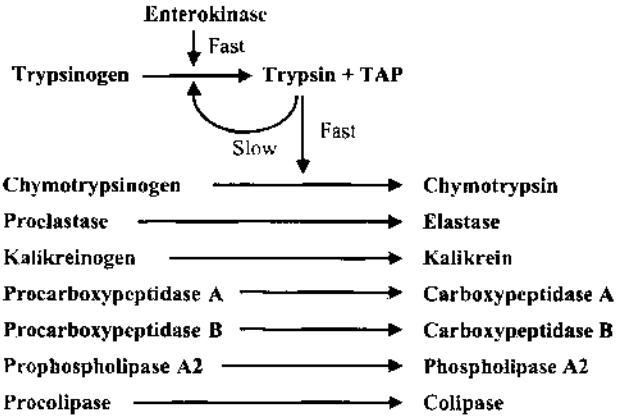


FIGURE 1 The pancreatic enzyme activation cascade. Trypsinogen(s) and other pancreatic secretory enzymes are secreted into the intestinal lumen as part of pancreatic juice. Trypsinogen is activated by enterokinase, which cleaves an amino-terminal activation peptide (TAP). Active trypsin then cleaves and activates all of the other pancreatic proteases, a phospholipase, and colipase, which is necessary for the physiological action of pancreatic triglyceride lipase.

 

lysosomal proteases that are active at low pH, but these are normally kept in a separate compartment in the cell. Activation of trypsinogen by cathepsins is thought to play a role in the genesis of acute pancreatitis.

## ENZYMATIC ACTION OF TRYPSIN

This enzymatic activity of trypsin is directed at the carboxyl moiety of the basic amino acid residues lysine and arginine in proteins. Physiologically, trypsin is an endopeptidase, breaking down proteins and large peptides into small peptides. It is a serine protease with an active site that contains a Ser, His, Asp catalytic triad that is shared with other serine proteases. Its specificity is the result of a unique binding pocket that contains two glycine residues. There are a number of natural and synthetic inhibitors that will inactivate trypsin either reversibly or irreversibly. Trypsins are active over a wide pH range from 6 to 9 and are most active at pH 7.5–8.5. Calcium ion enhances trypsin activity but is not essential. Trypsins can be assayed with low-molecular-weight substrates possessing an acylarginine ester or an amide structure where activity is measured as a result of a colored or fluorescent product. Trypsinogen in plasma can also be measured by radioimmunoassay or enzyme-linked immunosorbent assay, and a urinary dipstick sensitive to trypsinogen-2 is being evaluated for use in diagnosis of acute pancreatitis.

Recently, hereditary pancreatitis has been shown to be associated with specific mutations in cationic trypsinogen or PSTI. These mutations result in reduced inactivation of trypsin and are believed to lead to premature activation of trypsin in the pancreas when associated with other provocactive events.

### See Also the Following Articles

Pancreatic Digestive Enzymes • Pancreatic Enzyme Secretion (Physiology) • Pancreatitis, Hereditary

### Further Reading

Lowe, M. E. (1993). The structure and function of pancreatic enzymes. *In* "Physiology of the Gastrointestinal Tract" (L. R. Johnson, ed.), 3rd Ed., Raven Press, New York.

Rinderknect, H. (1993). Pancreatic secretory enzymes. *In* "The Pancreas: Biology, Pathobiology and Disease" (V. L. W. Go, et al., eds.), pp. 219–251. Raven Press, New York.

# Tumor Necrosis Factor-α (TNF-α)

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**caspases** Proteases that operate in a cascade to initiate programmed cell death.

**chemokine** A chemotactic cytokine, i.e., a secreted polypeptide hormone that promotes the migration of cells along a concentration gradient.

**cytokine** A secreted polypeptide hormone that interacts with cell surface receptors to activate immune and other mechanisms.

**ectodomain** The extracellular portion of a molecule that spans the plasma membrane.

**mitogen-activated protein kinases** Enzymes involved in the transmission of signals from cytokine and other receptors to downstream transcription factors.

**transcription factor** An intracellular protein that regulates gene transcription.

Tumor necrosis factor-α (TNF-α) is one member of a superfamily of related cytokines. This cytokine is synthesized by cells and released into the extracellular space. Through the interaction with specific cell surface receptors on target cells, TNF-α initiates cascades of intracellular events that affect cellular metabolism, viability, and gene expression. The net result of these effects is highly variable, depending on the cell type and on the influence of other factors. In general, TNF-α induces innate immune mechanisms and thereby promotes inflammation, but it is also a critical regulator of cell survival. Elevated concentrations of TNF-α are characteristic of many chronic inflammatory diseases. Strategies to inhibit the biological functions of TNF-α have proven

effective in the control of certain of these diseases, notably Crohn's disease and rheumatoid arthritis.

## INTRODUCTION

Tumor necrosis factor α (TNF-α) was first identified as a soluble factor that induced death in transformed cells. Independently, a molecule known as cachectin, which induced weight loss when overexpressed in animals, was described. Cloning of the genes encoding TNF-α and cachectin revealed that these are in fact the same molecule. Subsequent studies over the past 20–25 years have revealed diverse and potent effects of TNF-α on cellular functions that result in critical roles for this cytokine in mammalian physiology and pathophysiology. The cloning of genes closely related to TNF-α has revealed that this cytokine is part of a larger superfamily of related molecules. Two receptors that mediate the biological functions of TNF-α have been identified. This article examines TNF-α with particular emphasis on the factors that regulate its release, its actions on cells, and its role in chronic inflammatory diseases.

### Synthesis and Secretion of TNF-α

Many cell types, including immune cells such as monocytes, macrophages, and lymphocytes, but also epithelial cells, endothelial cells, and connective tissue cells, can produce TNF-α. Under basal physiologic conditions, cells secrete very little TNF-α, but many stimuli can induce cells to release TNF-α. For example, stimulation by the pro-inflammatory cytokines interleukin-1, interferon γ, or TNF-α, infection by invasive microbes such as *Salmonella*, exposure to lipopolysaccharide from gram-negative bacteria, or engagement of the T-cell receptor can result in dramatic up-regulation of the release of TNF-α from various cell types. Numerous exogenous agents, such as glucocorticoids or cyclosporin, and endogenous proteins, including transforming growth factor-β and interleukin-10, can decrease the release of TNF-α from cells. Cells tightly control the release of TNF-α by the regulation of at least three distinct steps in the synthesis and secretion of this cytokine (Fig. 1).

### Regulation of Transcription of the TNF-α Gene

A promoter region of approximately 600 bp upstream of the TNF-α gene contains binding sites for at least five distinct transcription factors. Mutational analyses of this promoter have revealed important roles for activating protein-1, nuclear factor of activated

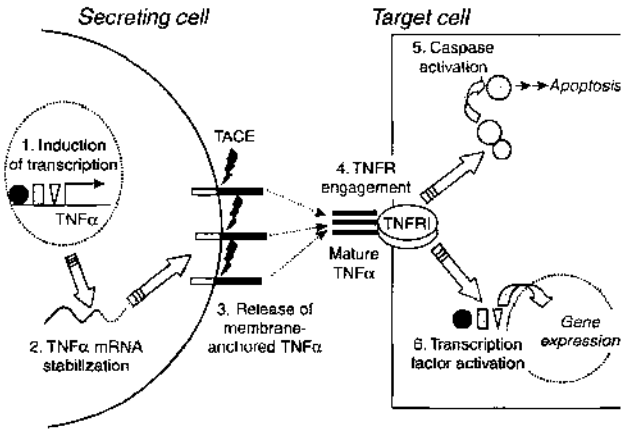


FIGURE 1 Model of TNF-α synthesis, secretion, and target cell stimulation. Several cellular mechanisms are involved in controlling the synthesis and secretion of TNF-α. A variety of transcription factors bind to the *TNF* promoter, leading to transcription of TNF-α mRNA (1). This mRNA is inherently unstable due to the presence of an AU-rich element in the 3′-untranslated region (dashed line). Stimulus-induced stabilization of TNF-α mRNA leads to greatly enhanced protein translation (2). When cells are stimulated to secrete TNF-α, the mature peptide is released by proteolytic cleavage of membrane-anchored TNF-α, by the action of TNF-α converting enzyme (TACE) (3). Released TNF-α forms homotrimers and binds to TNF receptors (TNFR) (4). Receptor engagement leads to clustering of the receptors, which facilitates the recruitment of numerous adapter and signaling molecules to the cytoplasmic tail of TNF receptors. Important downstream effects include the activation of caspase cascades (5), leading to apoptosis, and the activation of specific transcription factors (6), leading to target gene expression.

T cells, and nuclear factor κB (NF-κB) in the transcriptional regulation of TNF-α. Current concepts suggest that factors that induce TNF-α synthesis do so in part by stimulating the activity of these transcription factors, leading to increased rates of TNF-α transcription.

### Regulation of TNF-α Messenger RNA Stability

The 3′-untranslated region of the TNF-α messenger RNA (mRNA), like that of many other cytokines, contains an AU-rich element that destabilizes the transcripts. As a result, mechanisms within the cell degrade TNF-α mRNA unless it is specifically stabilized. As a result, very little template is available for ribosomal translation of TNF-α protein under basal conditions. Recent evidence suggests that the activation of mitogen-activated protein kinase pathways is involved in the stabilization of TNF-α mRNA, but the exact mechanisms of this process are currently unclear. In this model, efficient translation of TNF-α requires the stabilization of the mRNA by stimulus-induced mitogen-activated protein kinase activation. The importance

of this mechanism in the regulation of TNF-α is illustrated by the development of severe multisystem inflammation in mice genetically engineered to lack the 3′ AU-rich element and thus have stable, long-lived TNF-α mRNA.

### Inducible Ectodomain Shedding of Membrane-Bound TNF-α

TNF-α is synthesized as a 233-amino-acid protein that exists as a transmembrane molecule in which the biologically active portion is extracellular. In certain circumstances, such as the activation of T cells by antigen-presenting cells, this membrane-anchored form of TNF-α on the antigen-presenting cell can directly exert its biological activities by engaging TNF receptors on the T cell. More commonly, however, TNF-α is believed to act as a soluble hormone that diffuses to target cells after release from the cell of origin. Release of TNF-α requires proteolytic cleavage of the membrane-anchored form by TNF-α converting enzyme, leading to release from the cell of the mature 157-amino-acid soluble form of the cytokine. TNF-α molecules homotrimerize in the extracellular fluid and bind to their receptors on target cells.

## CELLULAR RESPONSES TO TNF-α

The biological effects of TNF-α are mediated by the binding of the cytokine to specific high-affinity cell surface receptors, TNF receptor-1 and TNF receptor-2. Both receptors are widely expressed. The majority of the biological effects of TNF-α (see below) are believed to be mediated by TNF receptor-1, except in immune cells where TNF receptor-2 is also important. Cytokine trimer binding to TNF receptors induces receptor clustering that is essential for activation of downstream signaling events (Fig. 1). After activation of TNF receptor-1 by TNF-α, a number of adapter and signaling molecules are recruited to the cytoplasmic domains of the receptor. A complex cascade of downstream signaling events ensues, resulting in two major phenomena: initiation of specific target gene expression by the activation of transcription factors and the cleavage of death proteins through the activation of caspases.

Target genes of TNF-α are diverse in function, but prominently include those that promote inflammation and inhibit apoptosis. Caspase activation results in the cleavage of death substrates, which leads to apoptosis. Thus, depending on the cellular context and on the effects of numerous additional factors, TNF-α stimulation of cells can lead to the activation of innate immune mechanisms and inflammation or can lead to apoptosis. NF-κB is central to the integration of cellular responses to TNF-α. In the presence of robust NF-κB activation by TNF-α, inflammatory responses are prominent. However, if NF-κB-dependent cell survival signals cannot be activated after TNF-α stimulation, the pro-apoptotic effects of TNF-α predominate.

## TNF-α IN PHYSIOLOGY AND DEVELOPMENT

*In vitro* and animal studies have defined a wide range of biological effects of TNF-α. At the molecular level, TNF-α induces the secretion of many cytokines, chemokines, growth factors, adhesion molecules, and enzymes that in general function to activate innate immunity. At the cellular and tissue levels, the effects of TNF-α depend not only on the cell type and the effects of other factors, but also on the local concentration of the cytokine. TNF-α induces leukocyte extravasation and activation of T and B lymphocytes and at high concentrations can induce apoptosis in some cells. Low concentrations may promote cell proliferation and the repair of tissue after injury. Experimental administration of TNF-α to animals induces fever, anorexia, and hypotension, mimicking endotoxic or septic shock.

The physiological functions of TNF-α have been explored by genetically engineering mice to lack TNF-α. These mice appear healthy and fertile, indicating that TNF-α is not essential for development or for normal physiological functions. However, TNF-α null mice lack mature B cell follicles and follicular dendritic cell networks in secondary lymphoid organs. In contrast, T-cell-rich areas are normal, suggesting an important role for TNF-α specifically in humoral immunity. Indeed, TNF-α null mice are highly susceptible to overwhelming infection with *Listeria monocytogenes*. Furthermore, these mice are somewhat resistant to developing endotoxic shock. These findings demonstrate that TNF-α is important in humoral immunity, in bacterial host defense, and in the responses to severe sepsis.

## TNF-α IN HUMAN DISEASE

Characterization of some of the *in vivo* biologic effects of TNF-α led to the examination of potential roles for this cytokine in human disease. The pathophysiology of many human diseases involves chronic inflammation in the diseased tissues and in many of these diseases, the circulating or tissue concentrations of TNF-α are elevated above control values. Elevated circulating concentrations of TNF-α have been observed in patients with severe sepsis syndromes, suggesting a potential

pathogenic role for this cytokine in septic shock. However, therapeutic attempts to neutralize the biologic activity of TNF-α by administration of a neutralizing antibody to patients with severe sepsis were not beneficial (Table I). TNF-α concentrations are increased in certain chronic inflammatory diseases, notably inflammatory bowel disease and inflammatory arthritides. Since TNF-α is such an important activator of innate immune mechanisms, therapeutic inhibition of the biological activity of TNF-α has therefore emerged as an attractive target in these chronic inflammatory diseases (Table I). The management of severe, active Crohn's disease has been revolutionized by the use of infliximab, a chimeric anti-TNF-α antibody. This antibody produces therapeutic benefit in up to 70% of Crohn's disease patients who were previously refractory to conventional therapies. Infliximab and etanercept, a TNF receptor-1:Fc fusion protein, are also highly effective in inflammatory arthritides. Inhibition of the biologic activity of TNF-α comes at a price, however. Patients treated with potent anti-TNF-α agents are susceptible to opportunistic infections, especially reactivation of latent tuberculosis, and certain viral infections, such as herpes zoster. Furthermore, case reports of patients developing a multiple sclerosis-like central nervous system demyelinating disease after receiving potent anti-TNF-α therapies have generated much concern. It is possible that in certain circumstances, or at low concentrations, TNF-α may have protective effects against some disease processes.

**TABLE I Efficacy of Potent Anti-TNFα Therapies in Human Diseases**

| |
|---|
| Yes (proven efficacious in randomized placebo-controlled trials) |
| Crohn's disease |
| Rheumatoid arthritis |
| Ankylosing spondylitis |
| Psoriatic arthritis |
| Psoriasis |
| Maybe (positive data from uncontrolled trials) |
| Ulcerative colitis |
| Pouchitis |
| Behçet's disease |
| Pyoderma gangrenosum |
| Vasculitis |
| No (negative randomized placebo-controlled trials) |
| Septic shock |

## See Also the Following Articles

**Crohn's Disease • Crohn's Disease, Pediatric • Hepatotoxins • TH1, TH2 Responses**

## Further Reading


Kollias, G. (1998). TNF-α. *In* "The Gene Knockout Facts Book" (T. W. Mak, ed.), Vol. 2, pp. 1033–1034. Academic Press, San Diego, CA.

Kontoyiannis, D., Pasparakis, M., Pizarro, T. T., Cominelli, F., and Kollias, G. (1999). Impaired on/off regulation of TNF biosynthesis in mice lacking TNF AU-rich elements: Implications for joint and gut-associated immunopathologies. *Immunity* **10**, 387–398.

McKusick, V. A. (2002). Tumor necrosis factor. Online Mendelian Inheritance in Man. Available at http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id = 191160.

Podolsky, D. K., and Fiocchi, C. (2000). Cytokines, chemokines, growth factors, eicosanoids, and other bioactive molecules in inflammatory bowel disease. *In* "Inflammatory Bowel Disease" (J. B. Kirsner, ed.), 5th Ed., pp. 191–207. W. B. Saunders, Philadelphia, PA.

Present, D. H., Rutgeerts, P., Targan, S., Hanauer, S. B., Mayer, L., van Hogezand, R. A., Podolsky, D. K., Sands, B. E., Braakman, T., DeWoody, K. L., Schaible, T. F., and van Deventer, S. J. (1999). Infliximab for the treatment of fistulas in patients with Crohn's disease. *N. Engl. J. Med.* **340**, 1398–1405.

Targan, S. R., Hanauer, S. B., van Deventer, S. J., Mayer, L., Present, D. H., Braakman, T., DeWoody, K. L., Schaible, T. F., and Rutgeerts, P. J. (1997). A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor for Crohn's disease. *N. Engl. J. Med.* **337**, 1029–1035.

Ware, C. F., Santee, S., and Glass, A. (1998). Tumor necrosis factor-related ligands and receptors. *In* "The Cytokine Handbook" (A. Thompson, ed.), 3rd Ed., pp. 549–592. Academic Press, San Diego, CA.

Zhang, M., and Tracey, K. J. (1998). Tumor necrosis factor. *In* "The Cytokine Handbook" (A. Thompson, ed.), 3rd Ed., pp. 515–548. Academic Press, San Diego, CA.

# Tyrosinemia

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**acute intermittent porphyria** One of a group of rare inherited disorders resulting from disturbance of the metabolism of the breakdown products of the red blood cell pigment (porphyrin). A prominent feature is intermittent attacks of abdominal pain.

**NTBC** Originally developed as an insecticide, this compound [2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione] was hypothesized, and then shown, to have clinical utility in the treatment of hereditary tyrosinemia type I.

**Hereditary tyrosinemia type I is an inborn error of tyrosine metabolism, resulting from mutations in the fumaryl acetoacetate hydrolase gene, and affects the liver, kidneys, and peripheral nerves. A variety of interventions developed over the past several decades have improved clinical outcome, including liver transplantation and, more recently, pharmacotherapy with 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione.**

## INTRODUCTION

Hereditary tyrosinemia type I (referred to as tyrosinemia throughout the remainder of this article) is an autosomal recessive inborn error of metabolism that affects the liver, kidneys, and peripheral nerves. The disease results from deficiency in the enzyme fumaryl acetoacetate hydrolase (FAH), which is involved in the metabolism of tyrosine (Fig. 1). Tyrosinemia patients were first reported in the medical literature in the 1950s. Early outcomes were generally poor, with most patients succumbing in infancy or childhood. Over the past several decades, a variety of interventions have been developed, including dietary modification, liver transplantation, and prenatal screening. More recently, pharmacotherapy with the drug NTBC [2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione] has resulted in significant improvement in the natural history of this disease. This article reviews the epidemiology, genetics, clinical presentation, pathogenesis, diagnosis, and management of tyrosinemia.

## EPIDEMIOLOGY AND GENETICS

Tyrosinemia is caused by deficiency of FAH (EC 3.7.1.2), the last enzyme in tyrosine catabolism. Heterozygotes

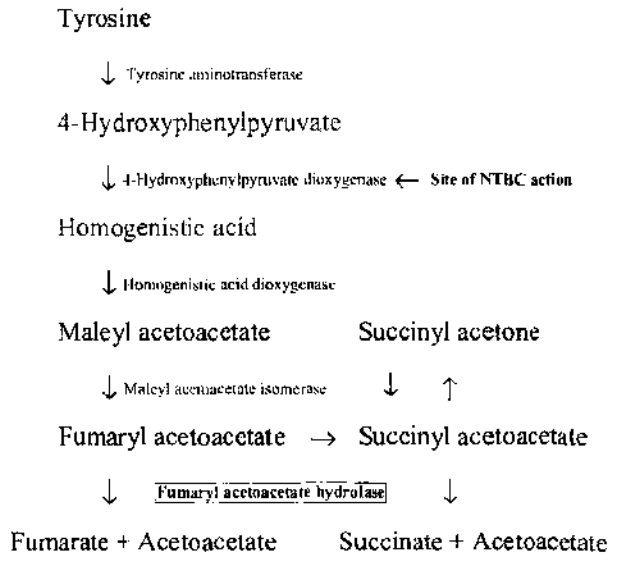


**FIGURE 1** Tyrosine degradation pathway. The last step in tyrosine metabolism is catalyzed by the enzyme fumaryl acetoacetate hydrolase, which is mutated in hereditary tyrosinemia type I. This leads to increased production of metabolites including maleyl acetoacetate, fumaryl acetoacetate, succinyl acetoacetate, and succinyl acetone.

are clinically and biochemically normal. The gene encoding FAH (GenBank Accession No. NM_000137) maps to chromosome 15q23–q25 and encodes a 419-amino-acid protein, present as a homodimer within the cytosol of hepatocytes.

### Epidemiology

The estimated worldwide incidence of tyrosinemia is 1 in 100,000 to 120,000. However, a much higher incidence has been recognized in northern Europe and Quebec, Canada. In the Saguenay-Lac-Saint-Jean area of Quebec, the carrier frequency of tyrosinemia is 1 in 20 and the frequency of disease in live births is 1 in 2000. Overall, the frequency of affected live births in Quebec is ~1 in 20,000. Because of this, Quebec has instituted routine prenatal testing. Tyrosinemia also occurs in ethnic groups other than French Canadian and Scandinavian.

 

### Mutations in FAH

At least seven different mutations in FAH have been identified in patients with tyrosinemia. Most mutant alleles in the Saguenay-Lac-Saint-Jean population contain a single common splice mutation (designated IVS12+5g-a). Although this mutation can also occur in patients from other ethnic backgrounds, different mutations may be more prevalent in certain backgrounds (e.g., W262X in Finns and Q64H in Pakistanis). Genotype–phenotype correlations have suggested that severe mutations resulting in complete absence of FAH mRNA and protein are associated with early-onset acute disease; however, very different clinical courses have been reported within affected members of the same family, suggesting that epigenetic and environmental factors must also play a role in determining outcome.

## CLINICAL PRESENTATION

Tyrosinemia should be considered in the differential diagnosis of any infant or child presenting with evidence of acute hepatocellular necrosis, conjugated hyperbilirubinemia, or decreased hepatic synthetic function of unknown etiology. Isolated or profound coagulopathy should also suggest the diagnosis. Children may also present with evidence of chronic disease with cirrhosis, nutritional rickets, renal tubular dysfunction, neurological crises, or failure to thrive. The differential diagnosis is that of liver failure in the infant and cirrhosis in the child or young adult. The natural history of tyrosinemia has been significantly modified by the development of prenatal screening for disease and pharmacological therapy with NTBC.

### Acute Presentation

In the absence of prenatal testing or prior to, patients usually come to medical attention with acute evidence of liver disease before 2 years of age. This presentation may be preceded by a catabolic stress such as viral illness or bacterial infection. Symptoms are nonspecific, e.g., growth failure, irritability, vomiting, hepato- or nephromegaly, ascites, or edema. A boiled cabbage odor, related to elevated serum methionine levels, may be noted. Occasionally, presentation was associated with a bleeding diathesis manifesting as bruising or epistaxis. Untreated, the disorder leads to liver failure within 1 year.

### Chronic Presentation

With chronic disease, liver dysfunction, renal tubular disease, and nutritional rickets may be present. A hallmark of the disease is the development of neurological crises that resemble acute intermittent porphyria. These are sudden-onset episodes of peripheral neuropathy with painful paresthesias, autonomic disturbance, extensor hypertonia, vomiting or paralytic ileus, and progressive weakness. Sometimes respiratory failure occurs, necessitating mechanical ventilation. The acute episode is followed by a variable recuperative period associated with weakness and paralysis. Cognition is not impaired and coma is not a feature of isolated neurological crisis but may suggest evolving hepatic encephalopathy. Tyrosinemia is also associated with a markedly increased risk of hepatocellular carcinoma even within the first 5 years of life with cases reported in patients less than 2 years of age. Renal disease is almost always present in patients with the chronic form of the disease, though its severity can be variable. Both tubular dysfunction and glomerular involvement occur. Rickets is the most common manifestation and is sometimes the primary medical problem. Tyrosinemia has also been associated with hypertrophic cardiomyopathy, as well as hypoglycemia associated with hyperinsulinism and pancreatic islet hypertrophy.

### Laboratory Biochemical, Imaging, and Histopathological Abnormalities

Laboratory findings typical of acute presentation may be notable for disproportionate coagulopathy without other findings of liver disease. Transaminases and conjugated bilirubin may be near normal or mildly elevated. Plasma tyrosine and methionine levels are often markedly elevated but this is not a specific finding. Serum α-fetoprotein levels can be extremely elevated, even in excess of 100,000 ng/ml. Urinary abnormalities are consistent with proximal renal tubular dysfunction with aminoaciduria and elevated levels of urinary succinyl acetone are diagnostic. Neurological crises are generally not associated with perturbations of liver biochemistries or increased levels of succinyl acetone from baseline. Intra-abdominal imaging with ultrasound or computed tomography may show hepatomegaly with increased hepatic echogenicity as well as nephromegaly and nephrocalcinosis. Liver biopsy specimens show hepatocellular inflammation and necrosis, steatosis, and lobular distortion with pseudoacinar formation and marked nodular regeneration.

## PATHOPHYSIOLOGY

Tyrosinemia results from deficiency of FAH, which catalyzes the last step in tyrosine degradation (Fig. 1). The molecular mechanisms responsible for the clinical

manifestations remain speculative. Hepatocellular and renal injury are thought to result from toxicity associated with *in vivo* accumulation of metabolites proximal to the enzyme defect, including fumaryl acetoacetate and maleyl acetoacetate and their by-products, succinyl acetoacetate and succinyl acetone. Fumaryl acetoacetate and maleyl acetoacetate are reactive unstable compounds that could theoretically consume the cellular machinery involved in protection from oxidative stress, thereby leading to tissue injury. Succinyl acetone is thought to be the most toxic intermediate. It can inhibit renal tubular transport, perhaps accounting for the proximal tubular dysfunction seen in this disease. Succinyl acetone has also been implicated as pathogenic in neurological crisis because it is a potent inhibitor of the enzyme δ-aminolevulinic acid dehydratase. This enzyme is involved in porphyrin biosynthesis, and its inhibition, which leads to the accumulation of δ-aminolevulinic acid, has been associated with neurotoxicity in acute intermittent porphyria, lead poisoning, and hereditary deficiency of the dehydratase.

Spontaneous reversion of the genetic defect in tyrosinemia has been shown to occur in nodular proliferating regions of tyrosinemic liver. In such regions, there is correction of the mutant FAH gene to wild type and detectable FAH enzyme activity. Fumaryl acetoacetate is known to be mutagenic, which may contribute to the increased frequency of genetic reversion in the diseased liver. The presence of revertant hepatocytes within proliferative nodules suggests that tyrosinemia induces a potent hepatic regenerative stimulus and that wild-type cells have a selective proliferative advantage over FAH-deficient cells.

Mouse models of FAH deficiency recapitulate much of the hepatic and renal pathophysiology that characterizes the human disease. In such mice, the disease phenotype can be reversed by re-introduction of a normal FAH transgene into the deficient background.

## DIAGNOSIS

Elevated succinyl acetone in blood, plasma, or urine is pathognomonic for the disease. The diagnosis can also be made by demonstration of absent or decreased FAH activity on enzymatic assay of liver tissue or skin fibroblasts. Molecular screening for common alleles can be performed in at-risk populations, though negative results do not exclude rare mutant alleles. Prenatal diagnosis is possible by analysis of succinyl acetone in amniotic fluid and by FAH assay of cultured amniocytes or chorionic villus cells. Neonatal screening based on analysis of succinyl acetone from dried blood on filter paper is performed in Quebec.

## TREATMENT

### NTBC

NTBC treatment has greatly improved survival, eliminated neurological crises, and reduced the need for liver transplantation during early childhood for patients with acute tyrosinemia. It is now the cornerstone of treatment. Originally developed as an insecticide, it was later found to be a potent inhibitor of 4-hydroxyphenylpyruvate dioxygenase (Fig 1). Thus, the hypothesis supporting its initial use in the treatment of tyrosinemia was that inhibition of this upstream enzyme in tyrosine metabolism would prevent accumulation of downstream, presumably toxic, metabolites, such as succinyl acetone. In 1992, Lindstedt and colleagues tested this hypothesis by treating five tyrosinemia patients with NTBC. Treatment led to marked clinical, histological, and biochemical improvement and caused no neurological, ocular, or cutaneous complications. Therapy markedly reduced α-fetoprotein levels, suggesting significantly decreased nodular regeneration in the diseased liver. The results from treatment of larger numbers of patients over 9 years have shown that the vast majority of patients do very well. For patients in whom treatment with NTBC was started early in life, only two cases (1%) of hepatocellular carcinoma during the first year of life have been reported. If NTBC is started later in the course of disease, there appears to be increased risk for the development of hepatic malignancy and management decisions must be made on an individual case-by-case basis.

### Dietary Restriction and Liver Transplantation

Prior to the development of NTBC, therapeutic intervention in tyrosinemia primarily involved dietary restriction of tyrosine and phenylalanine and liver transplantation. Hematin was used by some to treat neurological crises based on its ability to inhibit δ-aminolevulinic acid synthase.

Dietary restriction is still generally instituted at the time of diagnosis and continued throughout treatment with NTBC. The diet is stringent and based on a specialized formula that provides sufficient essential amino acids for growth but restricts tyrosine and phenylalanine. If the restriction is too great, growth failure, anorexia, and lethargy can result and so monitoring of growth and nutritional status while on the diet is important. Liver transplantation cures the metabolic liver disease and recurrent neurological crises and improves renal function. Prior to NTBC therapy, defining the optimal timing of transplantation was often challenging

owing to the high risk of development of hepatocellular carcinoma. Some would advocate transplantation early in infancy, whereas others adopted a more conservative approach. With the availability and success of NTBC in the management of tyrosinemia, liver transplantation is now likely to be restricted only to rare patients who present late or whose disease is severe and irreversible at the time of presentation. Nevertheless, NTBC therapy does not obviate the need for careful follow-up of affected patients and surveillance for hepatocellular carcinoma.

## ANALYSES IN MOUSE MODELS

Analyses in FAH-deficient murine models of tyrosinemia also show that NTBC has a significant effect on the course of disease, though the correction is not complete as mice continue to show accumulation of intermediate levels of succinyl acetone and some develop hepatocellular carcinoma. Whether human patients with tyrosinemia on NTBC are at continued risk for the development of hepatocellular carcinoma is unknown. Studies in the FAH-deficient mouse model have also shown that hepatocellular transplantation can correct the disease state by repopulation of diseased liver with normal hepatocytes. Repopulation occurs only in the diseased liver and not in the livers of NTBC-treated mice. These data suggest that hepatocellular transplantation may one day be useful in the treatment of tyrosinemia in people and, perhaps, the treatment of other cell autonomous metabolic liver diseases as well.

## See Also the Following Articles

**Carbohydrate and Lactose Malabsorption • Food Intolerance • Galactosemia • Glycogen Storage Disease • Hereditary Fructose Intolerance • Liver Transplantation**

## Further Reading

Berry, G. T. (2000). Genetic and metabolic hepatic disorders. 2. Disorders of amino acid metabolism. *In* "Pediatric Gastrointestinal Disease: Pathophysiology, Diagnosis, Management" (W. A. Walker, P. R. Durie, J. R. Hamilton, J. A. Walker-Smith, and J. B. Watkins, eds.), 3rd Ed., pp. 1072–1075. B. C. Decker, Lewiston, NY.

Gishan, F. K. (2003). Inborn errors of metabolism that lead to permanent hepatic injury. *In* "Hepatology: A Textbook of Liver Disease" (D. Zakim and T. Boyer, eds.), 4th Ed., pp. 1425–1430. W. B. Saunders, Philadelphia, PA.

Grompe, M. (2001). The pathophysiology and treatment of hereditary tyrosinemia type 1. *Semin. Liver Dis.* 21, 563–571.

Holme, E., and Lindstedt, S. (2000). Nontransplant treatment of tyrosinemia. *Clin. Liver Dis.* 4, 805–814.

Mitchell, G. A., Russo, P. A., Dubois, J., and Alvarez, F. (2000). Tyrosinemia. *In* "Liver Disease in Children" (F. J. Suchy, R. J. Sokol, and W. F. Balistreri, eds.), 2nd Ed., pp. 667–685. Lippincott Williams & Wilkins, Philadelphia, PA.

Teckman, J. H., and Perlmutter, D. H. (1999). Metabolic disorders of the liver. *In* "Pediatric Gastrointestinal Disease: Pathophysiology, Diagnosis, Management" (R. Wyllie and J. S. Hyams, eds.), 2nd Ed., pp. 590–591. W. B. Saunders, Philadelphia, PA.

# Ultrasonography

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**adjuvant chemotherapy** Chemotherapeutic treatment of malignancy administered after surgery or radiotherapy to reduce the risk of relapse.
**bolus** Intravenously injected dose of a contrast agent, administered rapidly to produce a short contrast effect.
**color Doppler** Colored display of blood flow.
**Doppler** Frequency shift caused by blood flow.
**echogenic** Returning a high level of echoes.
**elasticity imaging** Process in which the stiffness of a tissue under compression is turned into an image.
**endoscopy** Scans taken from within a body cavity, typically the esophagus or stomach, using specially designed small transducers.
**hydrocolosinography** Examination of the colon after it has been filled with fluid.
**microbubbles** Gas bubbles ranging in size from 1 to 10 μm that are used as contrast agents for ultrasound.
**spectral Doppler** Display of the constituent components of the Doppler signal over time.
**transjugular intrahepatic portosystemic shunt** Passage positioned so as to allow portal blood access to the hepatic veins or inferior vena cava, bypassing the liver in portal hypertension.

**Ultrasound has undergone very rapid developments in recent years; in addition to improved image quality and Doppler sensitivity, the introduction of contrast agents in the form of injectable microbubbles has expanded the horizons of ultrasound applications. Many of these advances have particular significance for gastroenterology.**

## GASTROINTESTINAL TRACT

Ultrasound is useful in all parts of the gastrointestinal tract, allowing imaging of the five-layered structure the wall throughout the entire tract. For the esophagus and stomach, endoscopic ultrasound (EUS) probes have been developed; EUS is an excellent compliment to endoscopy because it "sees" beyond the mucosa. EUS achieves a 75% accuracy in the local and nodal staging of carcinoma of the esophagus and is very reliable in differentiating gastric leiomyomas from carcinomas because the former have a characteristic appearance as well demarcated echo-poor masses. Staging of carcinoma in the stomach is less successful than in the esophagus.

Endoscopic systems are also useful for studying the anorectal region, especially for sphincter injuries. Magnetic resonance imaging (MRI) with intracavitary coils gives similar information in this important problem and is superior for detecting fistulas. For the remainder of the gut, transabdominal scanning with high-frequency transducers is used. Thickening of the colonic wall $>3$ mm is readily demonstrated and allows cancers to be detected as localized masses, in contradistinction to the extensive wall thickening in Crohn's disease, in which fistulous tracts and paracolonic abscesses can also be delineated. In ulcerative colitis, only the mucosal layer is thickened; the terminal ileum is selectively thickened in terminal ileitis, a common cause of right iliac fossa pain in young people in whom the associated regional lymphadenopathy may also be demonstrable. Diverticuli are seen as gas-containing structures lying within, or adjacent to, the colon wall. Intussusception produces a characteristic multilayered mass corresponding to the triplicated walls of the gut layers (Fig. 1). Ultrasound (US) can also be used

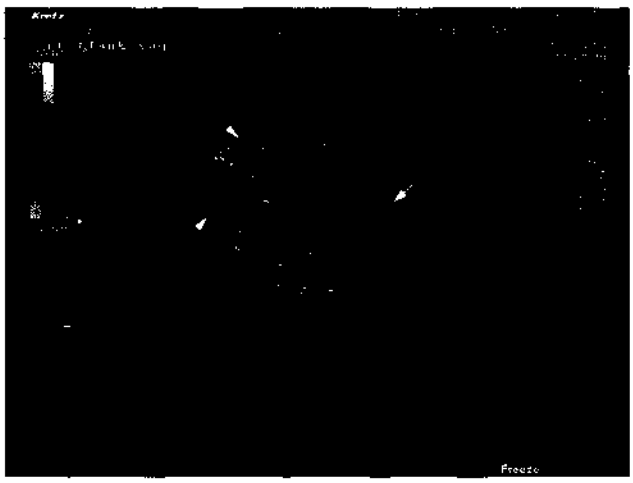


FIGURE 1 Intussusception. This patient presented with severe diffuse abdominal pain; ultrasound revealed a mass in the right flank into which the vascularized terminal ileum passes (arrow). Stretched around the hypovascular mass is a thin rim of stretched ascending colon (arrowheads). The mass proved to be cecal carcinoma, which had formed the lead of the intussusception.

to monitor hydrostatic reduction, thus limiting exposure to ionizing radiation.

Pyloric stenosis can often be diagnosed on clinical grounds, but in doubtful cases the thickened pyloric wall is easily detectable with US (Fig. 2). This, coupled with the demonstration of active gastric peristalsis that peters out as it reaches the pylorus, makes ultrasound a very reliable diagnostic tool. Another pediatric problem that is easily solved with US is malrotation of the small bowel. Using Doppler to determine the relative positions of the superior mesenteric artery and vein (SMA and SMV) by depicting their flow direction, the abnormal relationship of the artery and vein can be demonstrated.

The normal appendix can be demonstrated in some two-thirds of patients by using high-resolution transducers with graded compression to displace the gas that otherwise prevents acoustic access. The technique involves first localizing the cecal pole by tracing the ascending colon down into the right iliac fossa. Then, using a linear or curved array, gentle pressure is applied over several minutes to allow access to the appendix, which is seen as an elongated layered structure less than 7 mm in diameter. The inflamed appendix is thickened and the fecolith that is often present can be demonstrated as an echogenic nodule that casts an acoustic shadow. The inflammatory reaction produces an increase in Doppler signals (Fig. 3). Thickened omentum may be demonstrated as an amorphous mass of medium

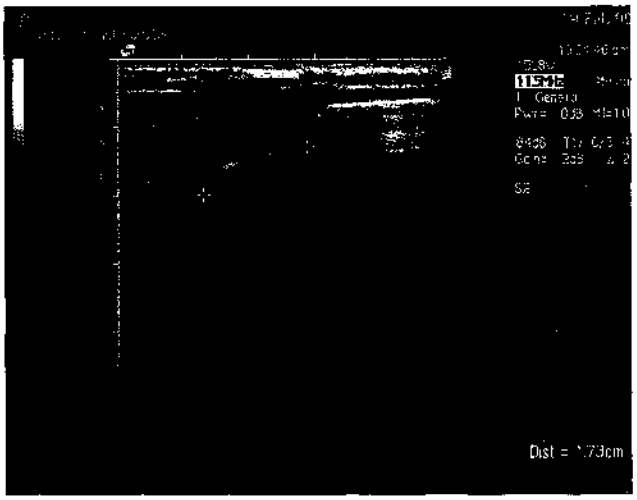


FIGURE 2 Pyloric stenosis. In a 6-week-old child who presents with projectile vomiting, the demonstration of hypertrophy of the pyloric canal is definitive. Here the pylorus measures 17 mm in length (normal, < 15 mm). In addition, on the real-time study, peristaltic waves could be seen advancing along the antrum but failing to move contents into the duodenum.

FIGURE 3 Appendicitis. In this patient with right iliac fossa pain, the hyperemic mass on ultrasound (arrowheads) corresponded with the point of maximum tenderness. The mass is the dilated inflamed appendix lying immediately inferior to the gas-containing cecum. There is no periappendicular collection to suggest an abscess. An uncomplicated acutely inflamed appendix was removed laparoscopically. (See Plate 1.)

echoes close to the appendix, whereas a perforation produces an adjacent fluid space. In right iliac fossa (RIF) pain, US can be used to diagnose terminal ileitis and distinguish it from gynecological causes.

Colonic polyps cannot be demonstrated by conventional ultrasound, but if the colon is first filled with water as a contrast agent, then exquisite images that clearly depict polyps down to 5 mm in diameter can be obtained using high-frequency transducers. However, the moderately invasive nature of "hydrocolosonography" and the fact that sessile or plaque-like tumors are not reliably visualized have limited the acceptance of the technique. In mesenteric angina, the tight stenosis or occlusion of the celiac axis and/or SMA produce localized fast flow on spectral Doppler or absent signals, respectively (Fig. 4).

## THE LIVER

The normal liver has a uniform texture of mid-gray reflectivity, interrupted by its blood vessels (Fig. 5). Diffuse liver diseases usually cause hepatomegaly; an exception is found in cases of advanced cirrhosis, for which shrinkage is typical, although judging liver size with ultrasound is very difficult. The commonest change in diffuse liver diseases is an increase in the echo level, providing an example of "bright liver," which is recognized by comparison with echoes from the renal cortex. Normally, the two are approximately

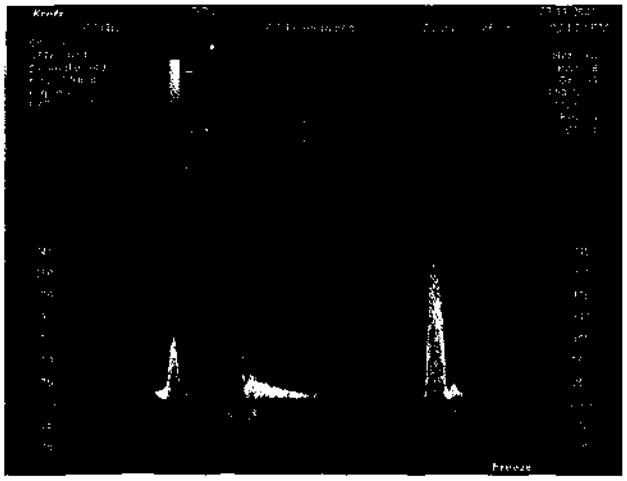


**FIGURE 4** Celiac axis stenosis. Celiac axis stenosis in isolation is rarely symptomatic because of the generous anastomoses in the gut's blood supply, but, because it usually occurs in arteriopaths, two or more of the arteries are often affected. The acceleration of the blood crossing the narrowing produces fast flow on the Doppler study (here rising to more than 4 m/second, shown in the lower panel) together with flow disturbance in the form of eddies that give slower flow signals as well as the very high-velocity signals. These result in a tracing in which all velocities are more or less equally represented, so that it appears as solid white from baseline to maximum velocity.

equally reflective, but in the bright liver, the renal cortex appears to be relatively dark. The bright liver as seen in a wide range of liver diseases, the commonest being fatty infiltration, but the list includes granulomatous and fibrotic conditions as well as cirrhosis and infiltrations by amyloid. The opposite pattern, "the dark liver," is less common, and is seen in conditions in which the amount of fluid in the liver is increased. Examples are acute hepatitis and congestive heart failure.

Cirrhosis is a progressive disease and the ultrasound findings reflect this; early on, there may be no demonstrable abnormalities or there may simply be an increase in reflectivity. In more advanced cases, the liver shrinks and the caudate lobe (segment 1) enlarges. The micro- or macronodularity of cirrhosis can be visualized in ascites, when the liver surface assumes a scalloped configuration (Fig. 6). Occasionally, regenerating nodules can be seen as ill-defined, patchy alterations in reflectivity, but usually the liver texture is merely slightly heterogeneous. The major changes demonstrable on ultrasound concern the blood flow, for which Doppler is well suited. The arterialization of the liver's supply makes the hepatic artery prominent, whereas flow in the portal vein may be normal or slow. In extreme cases, this is reversed, and in an intermediate stage, hepatic vein flow is balanced, being hepatofugal in one stage of the respiratory cycle and hepatopetal in another. Obviously, this situation of zero net flow is likely to lead to portal vein thrombosis and this may be demonstrated as echogenic material filling the vein together with an absence of Doppler signals. Subsequent recannalization or opening up of collateral vessels

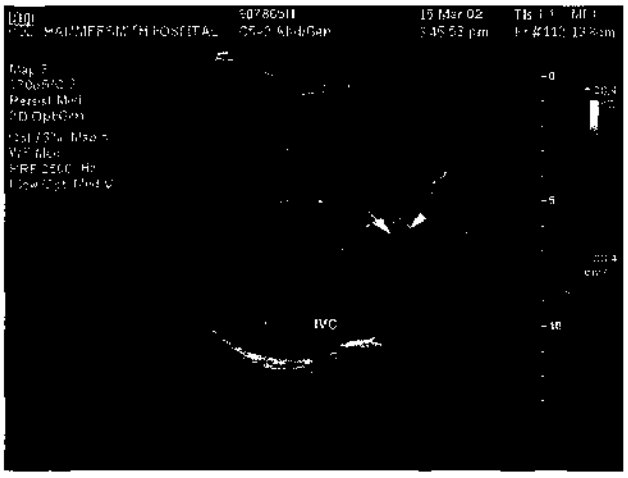



**FIGURE 5** Normal liver—porta hepatis. In a longitudinal section through the porta hepatis, the uniform texture of the liver parenchyma can be seen. In the color Doppler scan, the portal vein is depicted in red (see Plate 2), indicating flow toward the transducer. The hepatic artery (arrow), also in red, can be discerned anterior to it, and the dark circle (arrowhead) is the right hepatic duct seen in cross-section. The position of the duct represents a normal variant: usually it lies between the vein and the artery. IVC, Inferior vena cava.

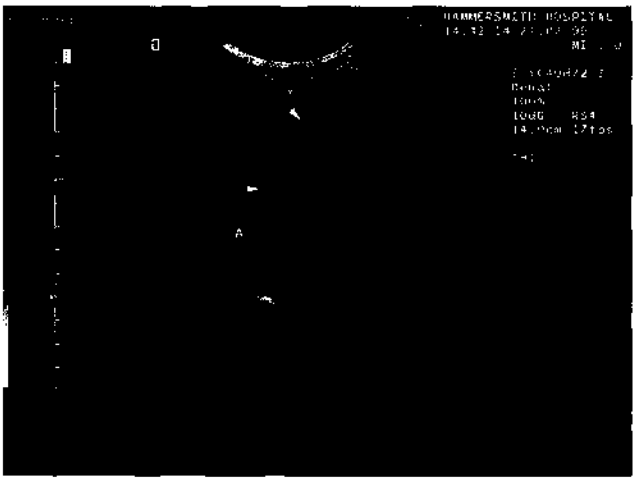



**FIGURE 6** Cirrhosis. In late cirrhosis, the irregular liver surface can be visualized against the echo-free ascites (A). In this case, the outline of macronodules (arrowheads) gives a scalloped border to the liver. Its echo texture is heterogeneous (compare with the normal, even texture of the normal liver in Fig. 5).

produces "cavernous transformation" of the portal vein, which gives a spectacular color Doppler picture of numerous small tortuous vessels in the porta.

The expected slowing of portal vein flow does not always occur because intrahepatic portosystemic shunts may form, and thus measurement of portal vein flow has not proved valuable in diagnosis or grading of cirrhosis. The most dramatic shunt is recannalization of the umbilical vein beyond the free margin of the liver (Fig. 7). Other portosystemic shunts may also be demonstrated, including retroperitoneal shunts and esophageal and spleno-esophageal varices. Because ultrasound demonstrates serosal varices whereas those seen on endoscopy are submucosal, the findings on these two modalities do not always correspond. Flow in transjugular intrahepatic portosystemic shunts (TIPSs) can usually be detected, but the shadowing from the metal of the stent and slow flow within the shunt may challenge the performance of even the best ultrasound scanner (Fig. 8). Here, administration of an ultrasound contrast agent can rescue an otherwise failed study.

Of the effects of portal hypertension, spleen size and ascites are very easily assessed by ultrasound. Supervening hepatocellular carcinoma may be obvious but small and multicentric lesions are difficult to demonstrate and some regenerating and hyperplastic nodules can produce masses that mimic hepatocellular carcinomas (HCCs). However, these benign lesions do not generally show Doppler signals, so hypervascular lesions are suspicious (Fig. 9). Sensitivity to hepatocellular


FIGURE 7 Recannalized umbilical vein. Recannalization of the umbilical vein produces this spectacular appearance on color Doppler (see Plate 3), with signals in the position of the ligamentum teres (arrow in A) flowing toward the umbilicus (U in B) and sometimes, as in this patient, on down into the pelvis [the change from red to blue codes for a relative change in flow direction, which is toward the probe superiorly (A), then parallel (B), and finally away from it (C)]. Often this spontaneous portosystemic shunt depressurizes the system and there are no other features of portal hypertension, such as ascites.

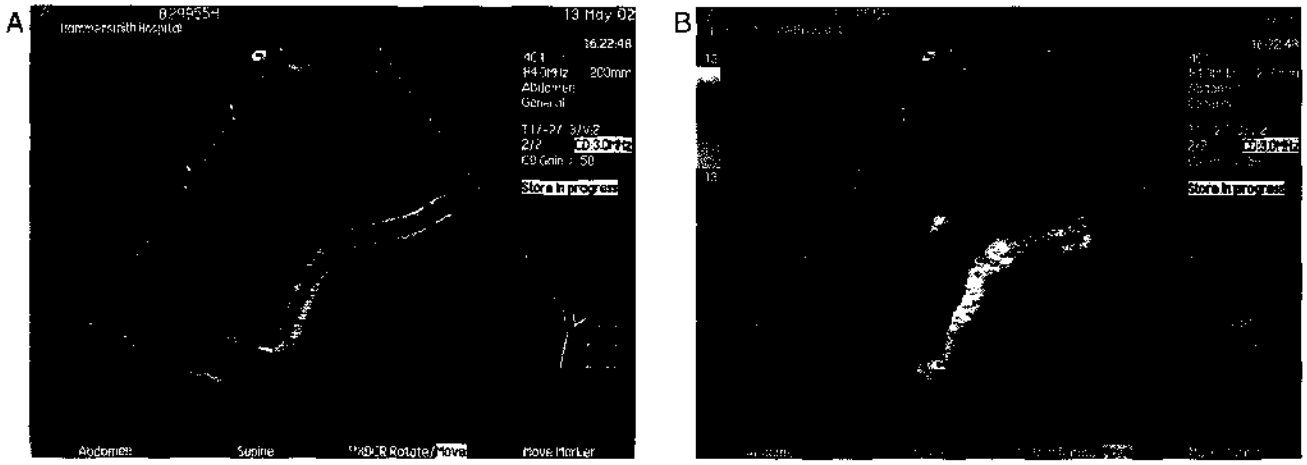



**FIGURE 8** This long transjugular intrahepatic portosystemic shunt is well visualized (A) and the flow is clearly seen to be toward the hepatic vein on the Doppler study (B). (See Plate 4.)

carcinomas is improved by microbubble contrast agents, which demonstrate the HCC vascularity in the arterial phase. In common with other malignancies, HCCs have a lower vascular volume compared to the liver and so they appear as defects in the late (sinusoidal or liver-specific) phase (Fig. 10). In schistosomiasis, a characteristic finding is prominence of the portal vein walls, corresponding to the per portal fibrosis of pipe stem cirrhosis. In the Budd–Chiari syndrome, lack of Doppler signals in the main hepatic veins is diagnostic. There is often reversed flow in the portal vein with ascites. If the thrombosed vessels recannalize, a thready meshwork replaces the normal pattern of three main veins (Fig. 11). Its microvascular equivalent, veno-occlusive disease, cannot be diagnosed with current ultrasound techniques.

## FOCAL LESIONS

A wide variety of focal liver lesions can be diagnosed by ultrasound, notably cysts, for which US is the most specific and sensitive test. Hydatid cysts have a variety of appearances, depending on the condition of their contents, but consistently have a prominent capsule that is lacking around simple cysts. In endemic countries, ultrasound-guided aspiration (perhaps with injection of a sclerosant) is widely used for symptomatic control with good safety.

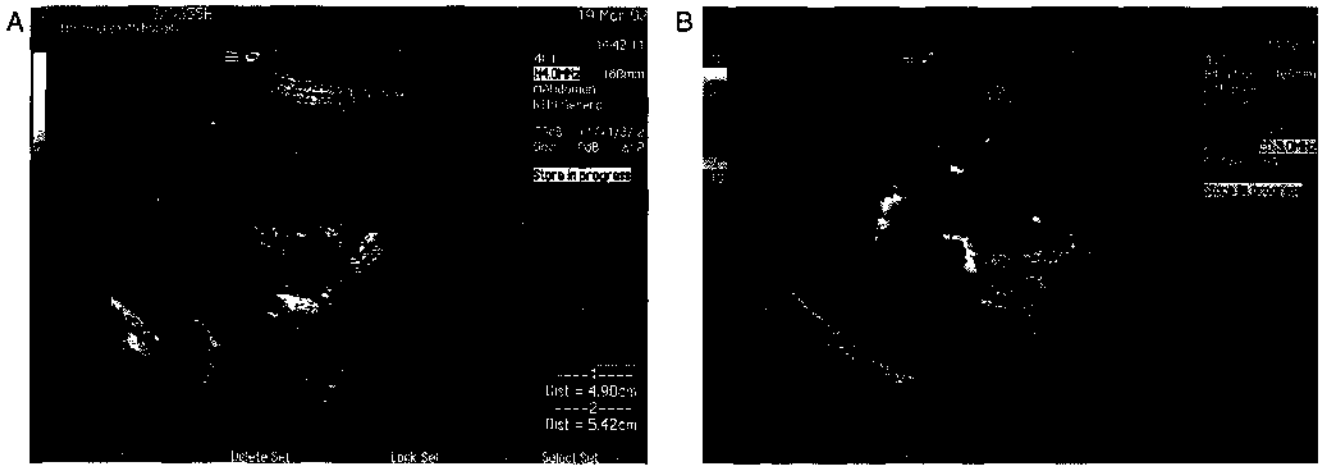



**FIGURE 9** Hepatocellular carcinoma. This irregular 5-cm mass in segment V in a cirrhotic patient (A) is suggestive of an hepatocellular carcinoma, and this is reinforced by the demonstration of numerous tortuous blood vessels within it on color Doppler (B). (See Plate 5.)

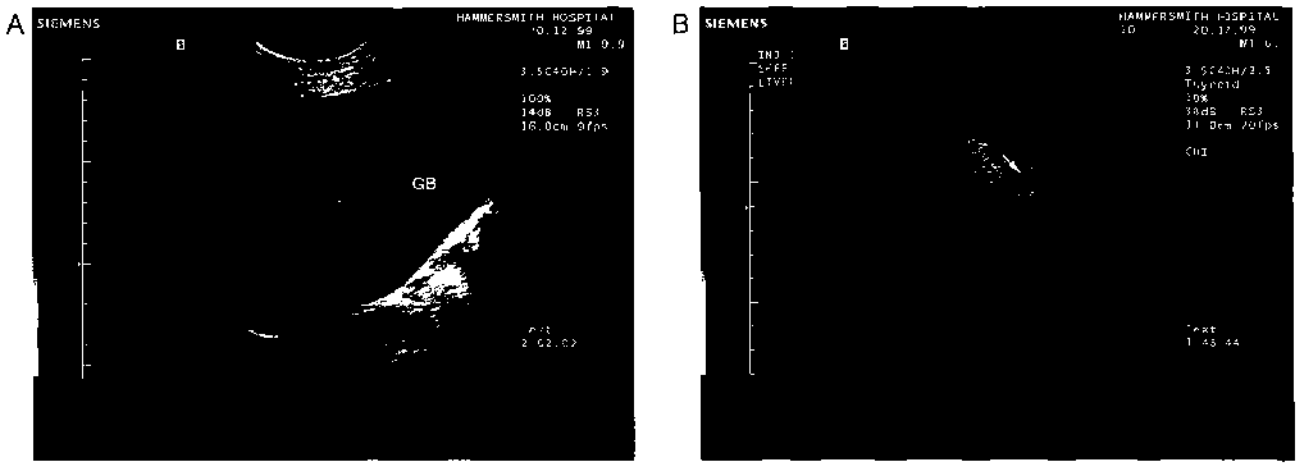



FIGURE 10 Occult hepatocellular carcinoma—contrast study. In this patient with cirrhosis, followup scans were performed to monitor the development of hepatocellular carcinoma. Only minor irregularity of the liver's texture was seen on the scan (A). He was entered into a phase 3 study of a new contrast agent, Sonazoid (Amersham, UK), and in the liver-specific phase a clear-cut lesion was revealed (arrow in B). Though the α-fetoprotein level was normal, an enhanced MRI study was performed and was read as normal. Three months later, the lesion became visible on unenhanced ultrasound and was confirmed on MRI and by biopsy to be hepatocellular carcinoma. Radiofrequency ablation was performed. GB, gallbladder.

Abscesses are typically seen as shaggy-walled cavities that are often multiple (Fig. 12). On Doppler, the hyperemia of the surrounding tissue is often obvious. However, in the initial stages of abscess formation, before pus has collected, a solid mass is found and the lesion can be very subtle.

Hemangiomas are the commonest benign liver tumor and typically appear as echogenic masses. On Doppler, they are hypovascular, only occasionally showing weak venous signals. In the late vascular phase after contrast injection, they typically show the same peripheral clumping that is characteristic on CT, with slow and often incomplete fill-in from the periphery over several minutes (Fig. 13). Focal nodular hyperplasia contains normal liver elements in an abnormal arrangement. Some have a vascularized central scar seen as an echo-poor streak with Doppler signals that typically radiate outward in a spoke-wheel fashion, and these arterial features are elegantly demonstrated after

FIGURE 11 Budd–Chiari syndrome. Recanalization of the thrombosed hepatic veins leads to a tangled pattern of vessels in the superior part of the liver. (See Plate 6.)

FIGURE 12 Liver abscess. A region of altered reflectivity (arrowheads) is seen in the left liver in this patient presenting with a fever. The appearance is typical of an abscess in the early (preliquefactive) phase of the development of an abscess. The ultrasound appearance is indistinguishable from metastatic disease, but the history usually provides the necessary clues and ultrasound-guided aspiration should be performed.

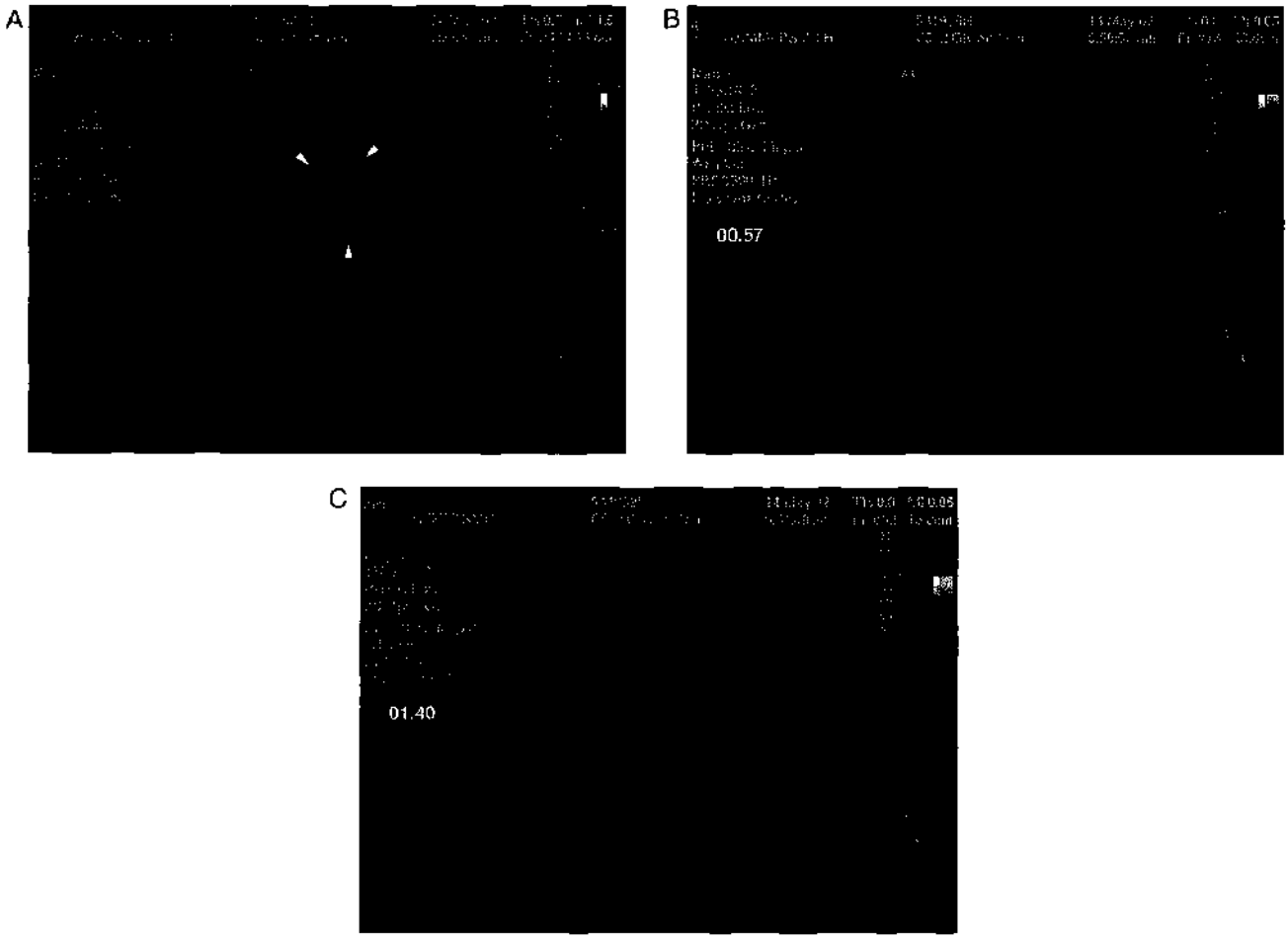



**FIGURE 13** Hemangioma contrast study. (A) This lesion in the inferior portion of segment V (arrowheads) in a patient with a known malignancy is suspicious for a metastasis because it is echo poor. (B) Soon after injection of a microbubble contrast agent (SonoVue, Bracco, Italy), clumpy peripheral filling is observed (contrast shown in red at 50 seconds after injection (see Plate 7); and thereafter there is progressive centripetal enhancement, until (C) at 1 minute, 40 seconds, when the lesion is almost completely enhanced and has become much less conspicuous. This dynamic pattern is typical of a hemangioma.

contrast enhancement. In the liver-specific phase of microbubble enhancement, their behavior is pathognomomic: they take up contrast strongly and so blend with the normal liver or occasionally even stand out with more intense signals (Fig. 14).

The variety of appearances of metastases on ultrasound is bewildering and remains largely unexplained (Fig. 15). Though there are trends (for example, echogenic metastases are typically gastrointestinal or urogenital in origin), it is not possible to tie particular patterns with the primary site. The success of ultrasound in liver staging has been exaggerated in the past, quoted figures of accuracies around 80% being calculated on a per patient basis rather than for individual lesions. These limitations have been highlighted by the improvement in detectability when ultrasound contrast agents are used. In several prospective studies, use of microbubble-specific modes allow the detection of lesions down to a diameter of 3 mm (Fig. 16). Though not yet perfected (a depth limitation of around 10 cm is an important limitation), this approach reveals more lesions than three-phase helical computed tomography (CT) and comes close to the sensitivity of MRI. Specificity is also addressed because malignancies, with their low blood volume, show as defects in the sinusoidal or liver-specific phases, and in some the feeding artery is obvious in the arterial phase (Fig. 17).

A particularly useful application of contrast agents is in evaluating the completeness of ultrasound-guided interstitial therapy: when all tumor appears to have

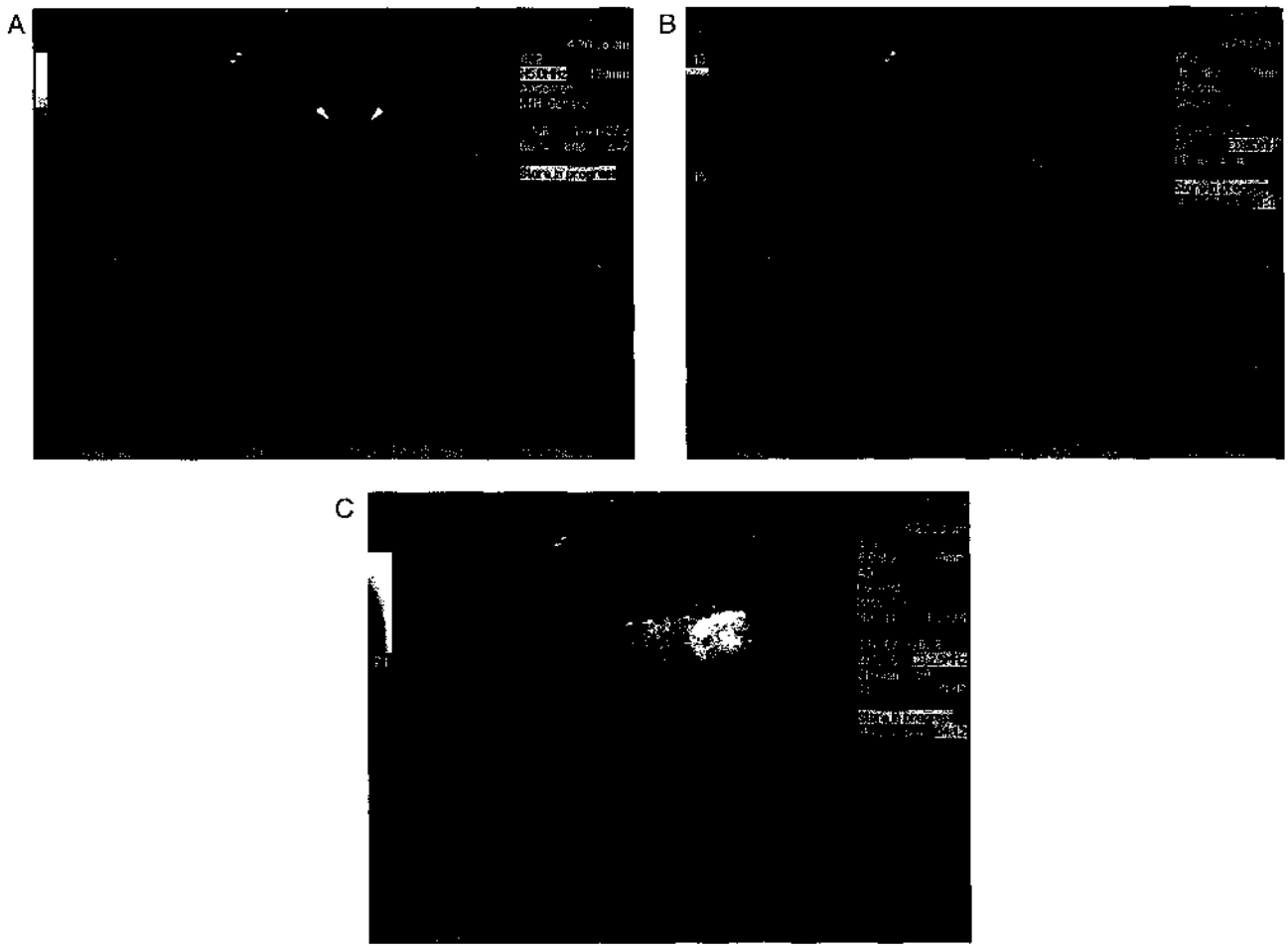



FIGURE 14 Focal nodular hyperplasia. (A) This focal lesion in the anterior part of segment 5 (arrowheads) was an incidental finding. (B) Its ill-defined margins and vascularity (color Doppler; see Plate 8) raised the suspicion of malignancy. However, following administration of the liver-specific contrast agent Levovist, nonlinear imaging shows that it takes up the agent to the same extent as the liver and it has disappeared (C). This makes the diagnosis of focal nodular hyperplasia most likely. The lesion remained unchanged a year later.

been destroyed, microbubbles often reveal residual portions of perfused tumor that can be ablated immediately, so that the patient does not have to be moved to CT. Microbubbles can also be used as tracers and in the liver the time taken for them to cross into the hepatic veins (normally 30 seconds or more, owing to the slow flow in the liver sinusoids) is shortened when there is arteriovenous shunting, as occurs in metastases and cirrhosis. This simple test seems to be able to detect occult metastases (for example, in colorectal cancer), and should prove useful in selecting those patients who would benefit from adjuvant chemotherapy. It is also very promising in differentiating uncomplicated chronic hepatitis from cirrhosis and this might avoid the frequent biopsies that are currently required to guide antiviral treatment in patients with hepatitis C (Fig. 18). In liver trauma (and that of other solid abdominal organs), conventional ultrasound is limited to detecting intraperitoneal bleeding. The advent of contrast agents that allow the microvasculature to be demonstrated promises to change that, and to provide useful imaging by the patient's bedside, without interrupting observations and supportive care (Fig. 19).

## BILIARY TREE

The exquisite sensitivity of ultrasound to liquid spaces has made it the primary imaging modality for the biliary tree and the standard test for gallstones (Fig. 20). Stone composition does not affect detectability. Occasional false positives occur when polyps are mistaken for

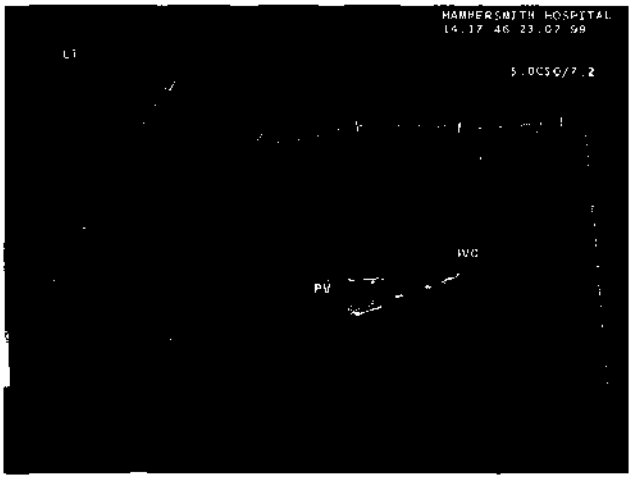



**FIGURE 15** Liver metastases. This extended field-of-view (Sciescape, Siemens) scan of an enlarged left liver exhibits numerous focal lesions of varying appearances, some echo poor, others echogenic. The patient had a carcinoma of the colon (minor scale divisions equal 1 cm). IVC, Inferior vena cava; PV, portal vein.

stones; their attachment to the gallbladder wall provides a clue.

In acute cholecystitis, major signs such as splitting of the thickened wall, tenderness localized to the gallbladder (the ultrasound Murphy's sign), and the presence of stones, coupled with minor signs such as dilatation of the gallbladder, are useful (Fig. 21). Ultrasound may also demonstrate alternative causes for right upper quadrant pain. Acalculus cholecystitis remains a difficult diagnosis but the demonstration of vascularity within the wall on Doppler can be useful. In critical cases, ultrasound can be used to direct a draining cannula as a holding measure.

Carcinoma of the gallbladder is seen as a mass, unfortunately often large, with invasion of the adjacent liver surface (Fig. 22). Hilar cholangiocarcinomas (Klatskin tumors) have infiltrating margins that are ill defined on imaging so it may be very difficult to determine the extent of the tumor. Here, microbubble contrast agents have contributed substantially because they outline the limits of the functioning liver, against which the tumor is clearly seen as a signal void, as with other liver malignancies.

Ultrasound is the primary imaging technique in obstructive jaundice because US sensitivity to fluid spaces is exploited. The diameter of the common duct is easily measured. Dilatation is evidence of obstruction and, provided it is appreciated that this anatomical feature may persist after relief of obstruction, is a highly reliable sign in the appropriate clinical setting (Fig. 23). Similar considerations apply to dilatation of the intrahepatic biliary tree, which produces the classic "parallel channel" and "double-barreled shot-gun" signs when the pairs of tubular structures are cut along or across, respectively (Fig. 24). Ultrasound is very sensitive for "surgical" jaundice, provided the history is taken into account, because the biliary tree may remain dilated indefinitely, even after relief of an obstruction. For the same reason, ultrasound cannot be used to tell whether a biliary stent has reobstructed, though the demonstration of aerobilia provides useful indirect

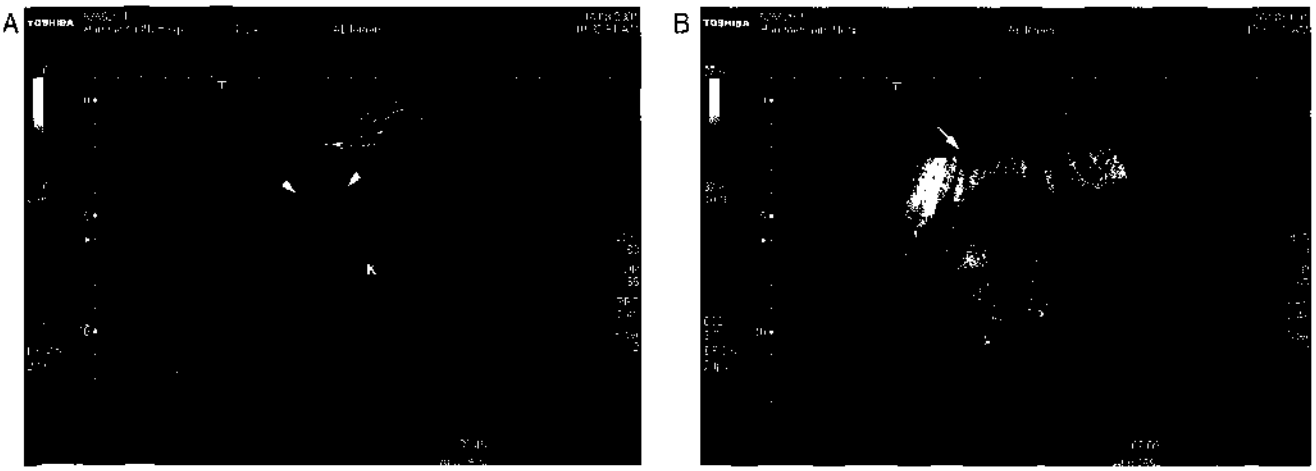



**FIGURE 16** Liver metastasis contrast study. (A) In this patient with a known colonic cancer, an obvious lesion compatible with a metastasis is seen in the inferior part of segment 5 (arrowheads); K, kidney. (B) In a registered image taken in the liver-specific phase after injection of the contrast agent Levovist (Schering, Berlin), using a liver-specific mode (Agent Detection Imaging) that shows the presence of contrast in color, this lesion is more clearly delineated, but an additional lesion that was not apparent before is also obvious (arrow). (See Plate 9.)

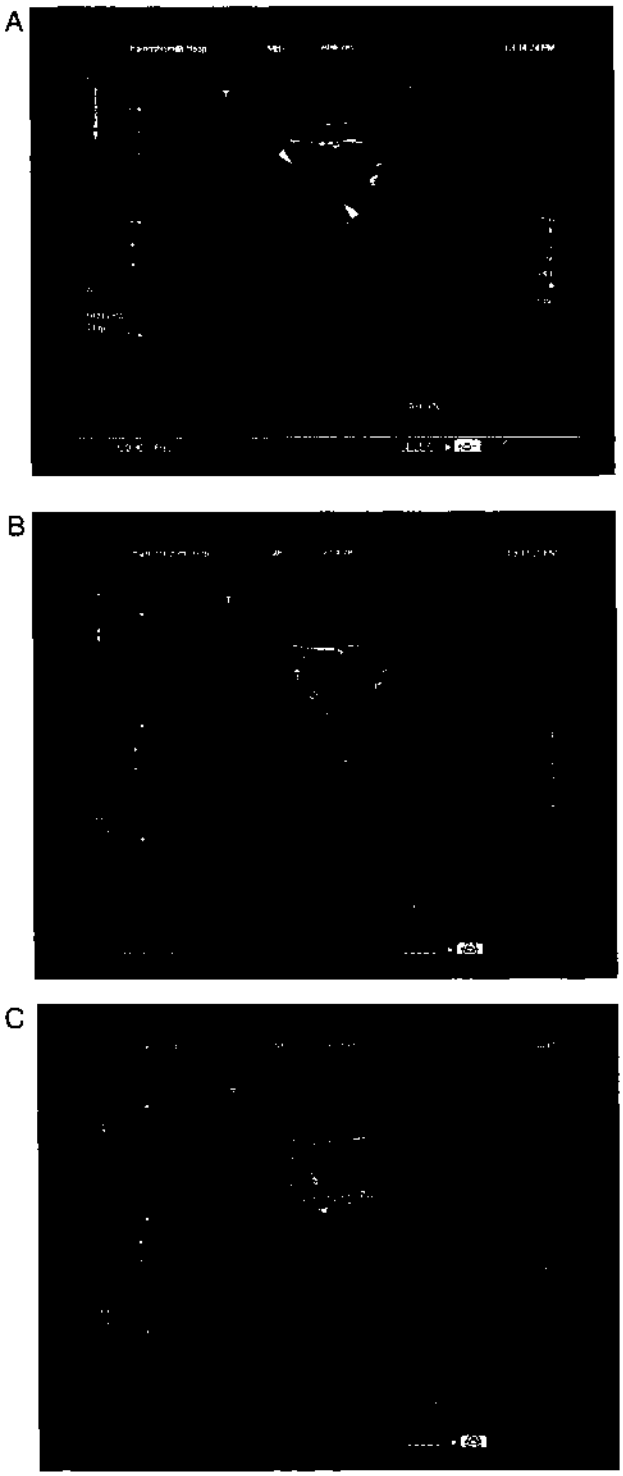



FIGURE 17 Liver metastasis contrast study. (A) A metastasis from a colonic carcinoma is seen as an echogenic mass (arrowheads) at the beginning of an injection of a microbubble contrast agent, SonoVue (7 seconds postinjection). (B) In the next image from the real-time sequence at 13 seconds postinjection (arterial phase), numerous small vessels enter the tumor from its periphery. In this microbubble-specific mode (Vascular Recognition Imaging, Toshiba, Tokyo), the contrast is depicted in green (see Plate 10) when it is stationary; the red and blue tints show moving microbubbles. (C) In the third frame, at 27 seconds, contrast is filling the liver parenchyma but the metastasis, with its low vascular volume, is highlighted as a signal void.

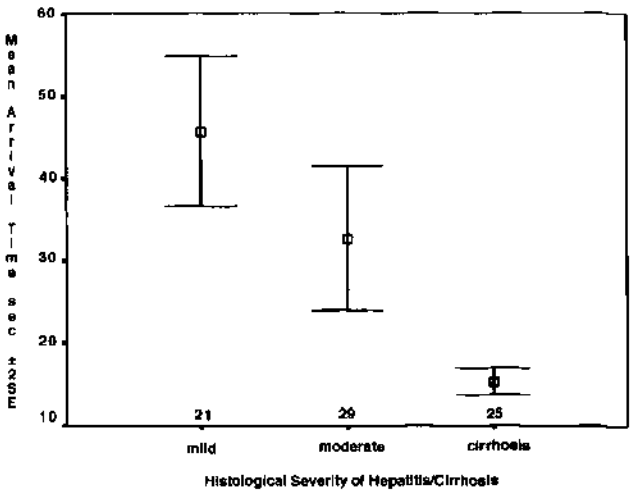



FIGURE 18 Hepatic vein arrival time. By noting the arrival of a bolus of a contrast agent in the hepatic veins, the delay from the moment of injection can be measured. When arteriovenous shunts develop in the liver, the arrival time is shortened from its normal of around 45 seconds. This test can detect the onset of cirrhosis in patients with chronic hepatitis showing mild and moderate changes in necroinflammatory scores on histology. The numbers above the *X* axis refer to the numbers of cases. Courtesy of Dr. Adrian Lim.

evidence of patency. Ultrasound can usually indicate the level of an obstruction by demonstrating the lowest point of dilatation, but is less useful in determining the cause, mainly because strictures cannot be detected, but also because many stones simulate soft tissue masses with no shadowing.

## PANCREAS

Long considered a challenge for ultrasound, the normal pancreas can usually be imaged, at least in part, by a combination of modern equipment and graded compression, using the probe to displace bowel gas (Fig. 25). Oral contrast agents may further improve access in the epigastrium, whereas the pancreatic tail can be imaged using the spleen as a window. The pancreas is relatively echogenic in the adult, though the uncinate process commonly retains the lower levels of echo intensity typical of the child's pancreas. The

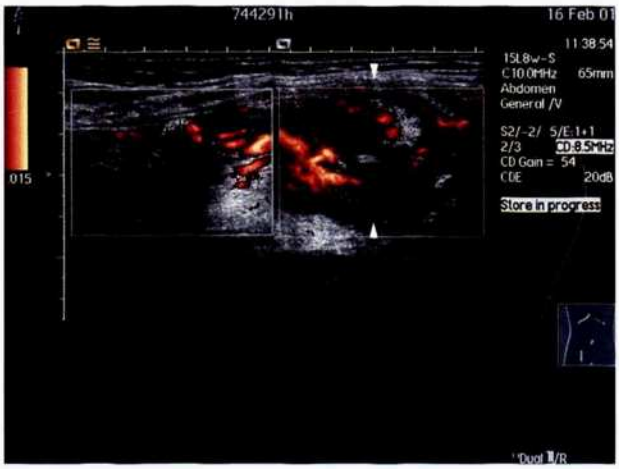



**Plate 1** Appendicitis. In this patient with right iliac fossa pain, the hyperemic mass on ultrasound (arrowheads) corresponded with the point of maximum tenderness. The mass is the dilated inflamed appendix lying immediately inferior to the gas-containing cecum. There is no periappendicular collection to suggest an abscess. An uncomplicated acutely inflamed appendix was removed laparosopically.

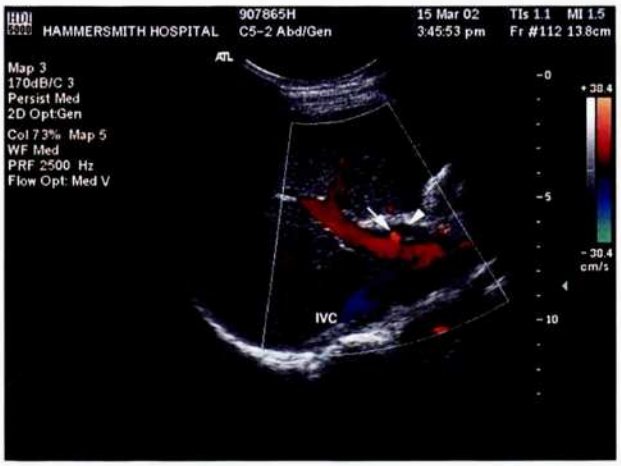



**Plate 2** Normal liver—porta hepatis. In a longitudinal section through the porta hepatis, the uniform texture of the liver parenchyma can be seen. In the color Doppler scan, the portal vein is depicted in red, indicating flow toward the transducer. The hepatic artery (arrow), also in red, can be discerned anterior to it, and the dark circle (arrowhead) is the right hepatic duct seen in cross-section. The position of the duct represents a normal variant: usually it lies between the vein and the artery. IVC, Inferior vena cava.

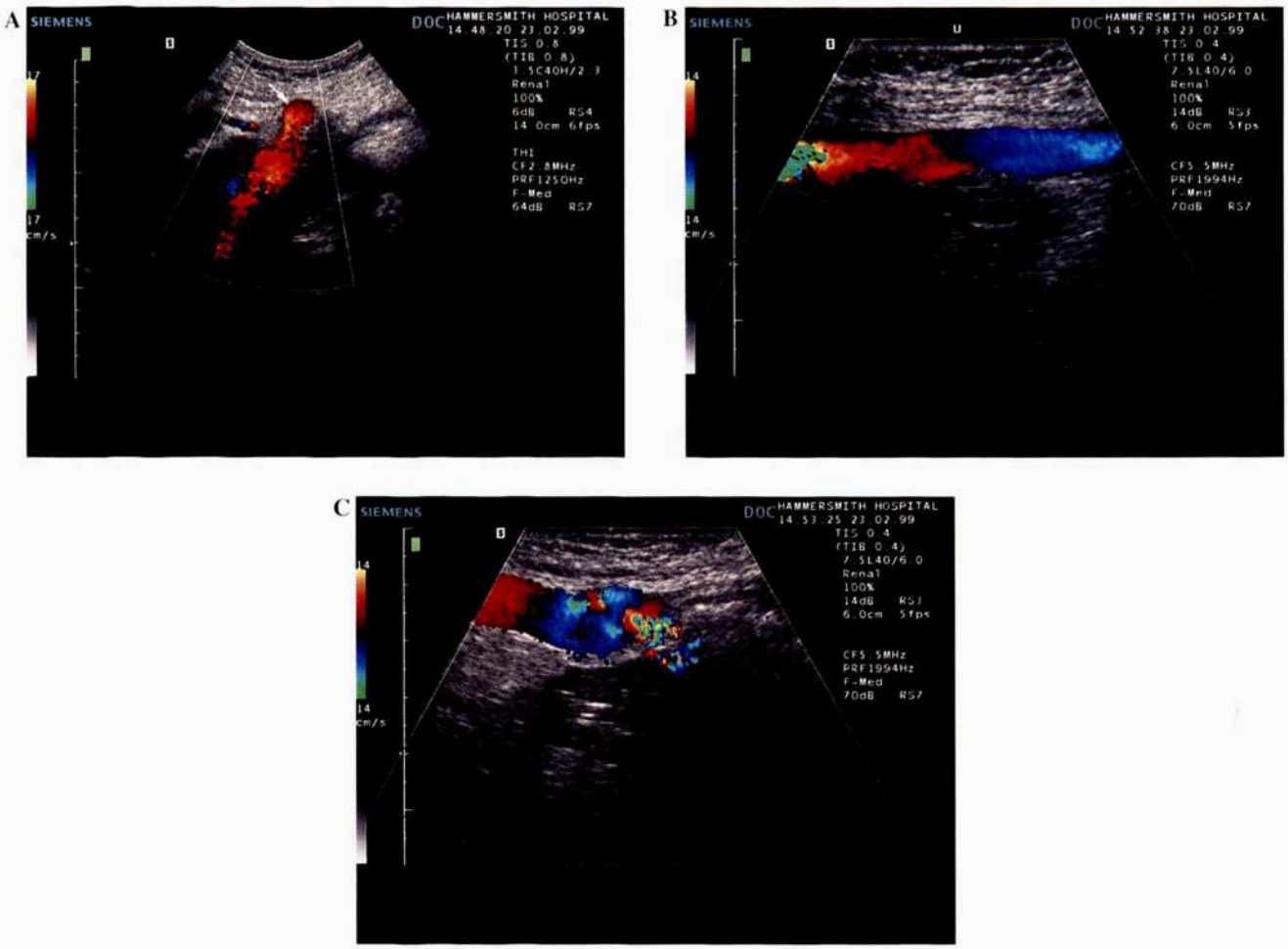



**Plate 3** Recannalized umbilical vein. Recannalization of the umbilical vein produces this spectacular appearance on the color Doppler, with signals in the position of the ligamentum teres (arrow in A) flowing toward the umbilicus (U in B) and sometimes, as in this patient, on down into the pelvis [the change from red to blue codes for a relative change in flow direction, which is toward the probe superiorly (A), then parallel (B), and finally away from it (C)]. Often this spontaneous portosystemic shunt depressurizes the system and there are no other features of portal hypertension, such as ascites.

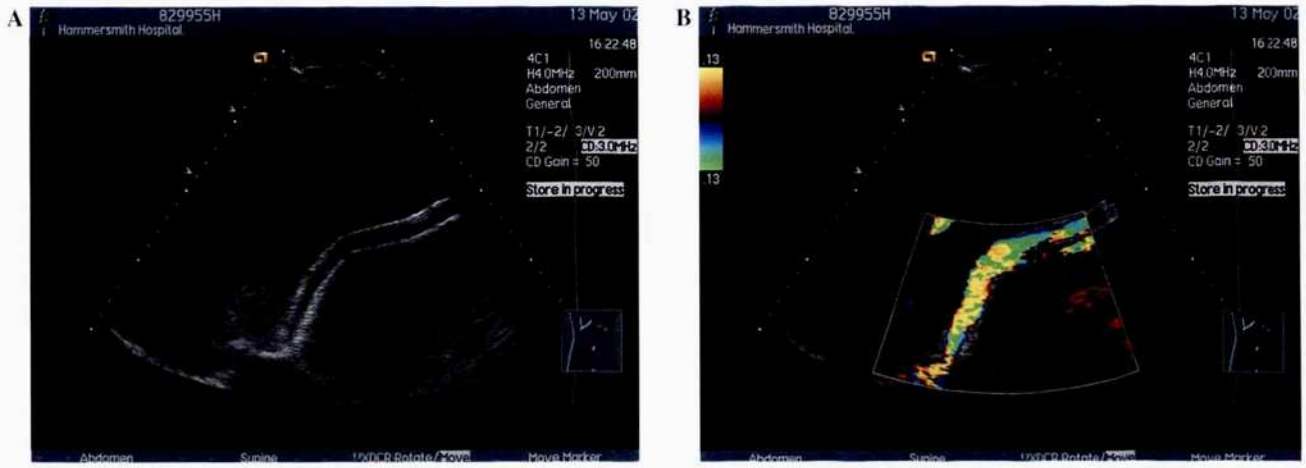



**Plate 4** This long transjugular intrahepatic portosystemic shunt is well visualized (A) and the flow is clearly seen to be toward the hepatic vein on the Doppler study (B).

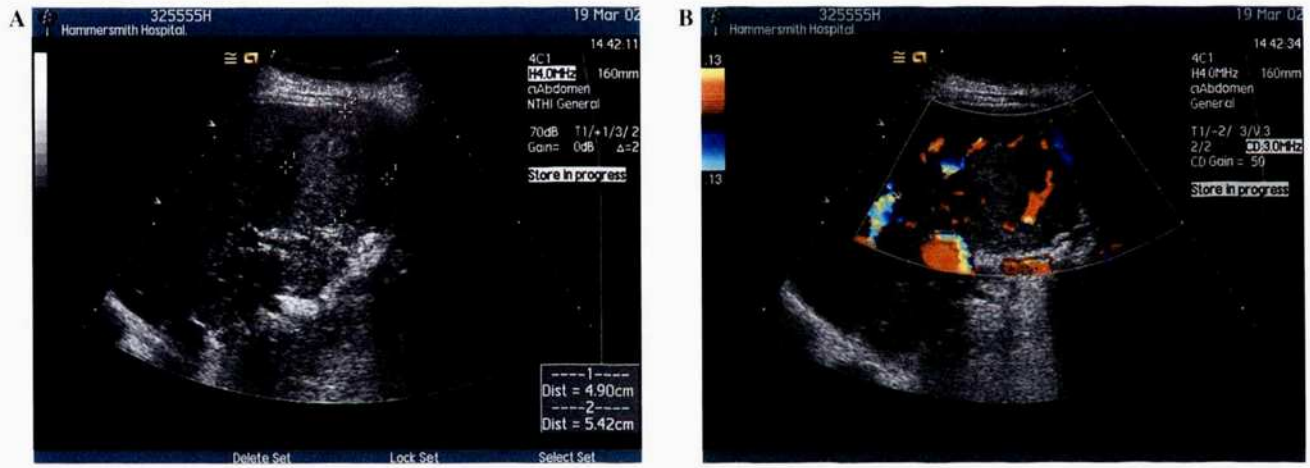



**Plate 5** Hepatocellular carcinoma. This irregular 5-cm mass in segment V in a cirrhotic patient (A) is suggestive of an hepatocellular carcinoma, and this is reinforced by the demonstration of numerous tortuous blood vessels within it on color Doppler (B).

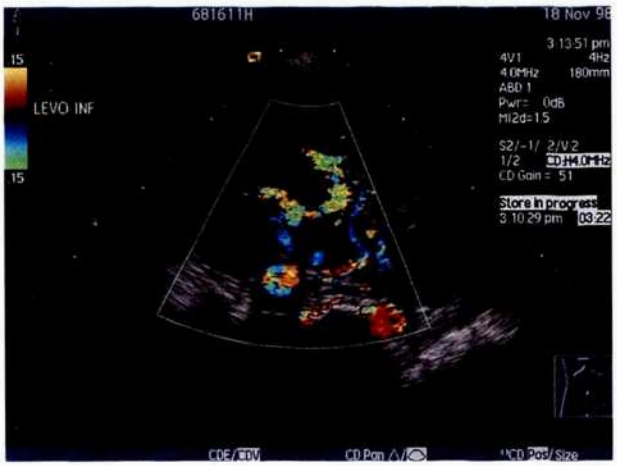
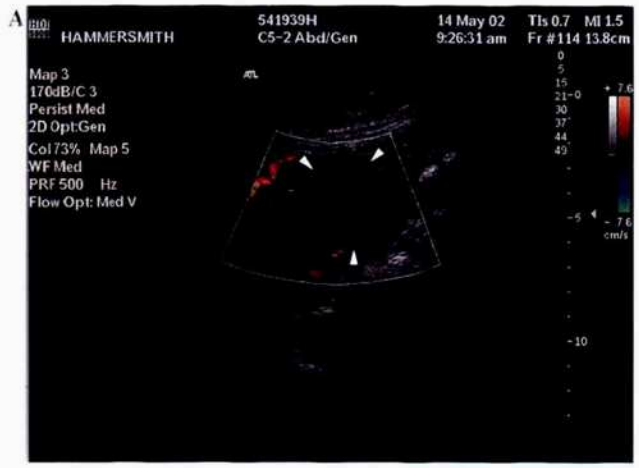
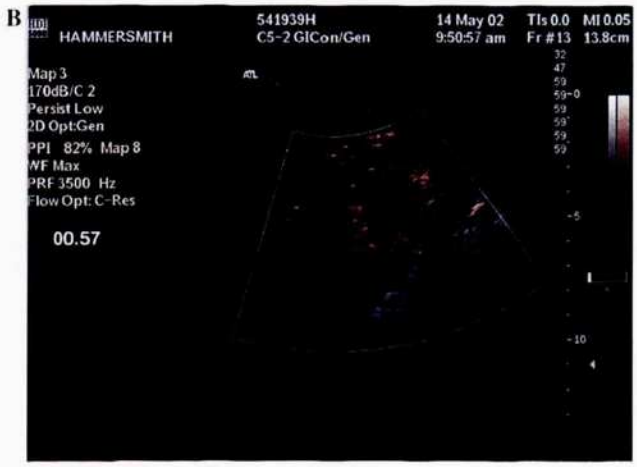
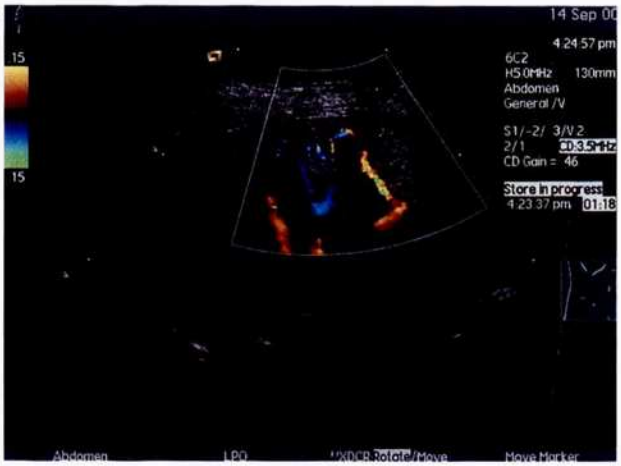


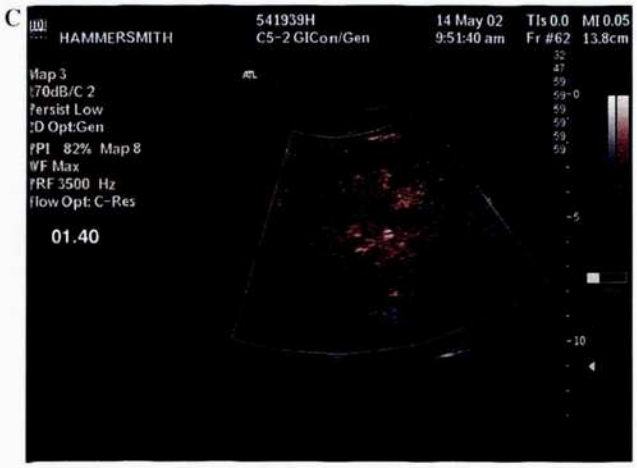

**Plate 6** Budd–Chiari syndrome. Recannalization of the thrombosed hepatic veins leads to a tangled pattern of vessels in the superior part of the liver.







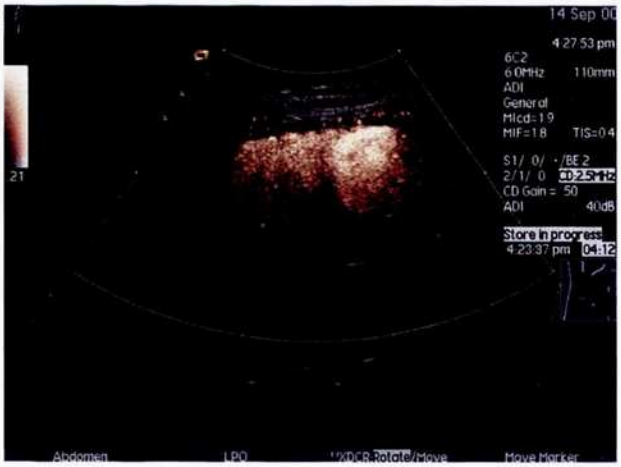




**Plate 7** Hemangioma contrast study. (A) This lesion in the inferior portion of segment V (arrowheads) in a patient with a known malignancy is suspicious for a metastasis because it is echo poor. (B) Soon after injection of a microbubble contrast agent (SonoVue, Bracco, Italy), clumpy peripheral filling is observed (contrast shown in red at 50 seconds after injection; and thereafter there is progressive centripetal enhancement, until (C) at 1 minute, 40 seconds, when the lesion is almost completely enhanced and has become much less conspicuous. This dynamic pattern is typical of a hemangioma.

**Plate 8** Focal nodular hyperplasia. (A) This focal lesion in the anterior part of segment 5 (arrowheads) was an incidental finding. (B) Its ill-defined margins and vascularity (color Doppler) raised the suspicion of malignancy. However, following administration of the liver-specific contrast agent Levovist, nonlinear imaging shows that it takes up the agent to the same extent as the liver and it has disappeared (C). This makes the diagnosis of focal nodular hyperplasia most likely. The lesion remained unchanged a year later.

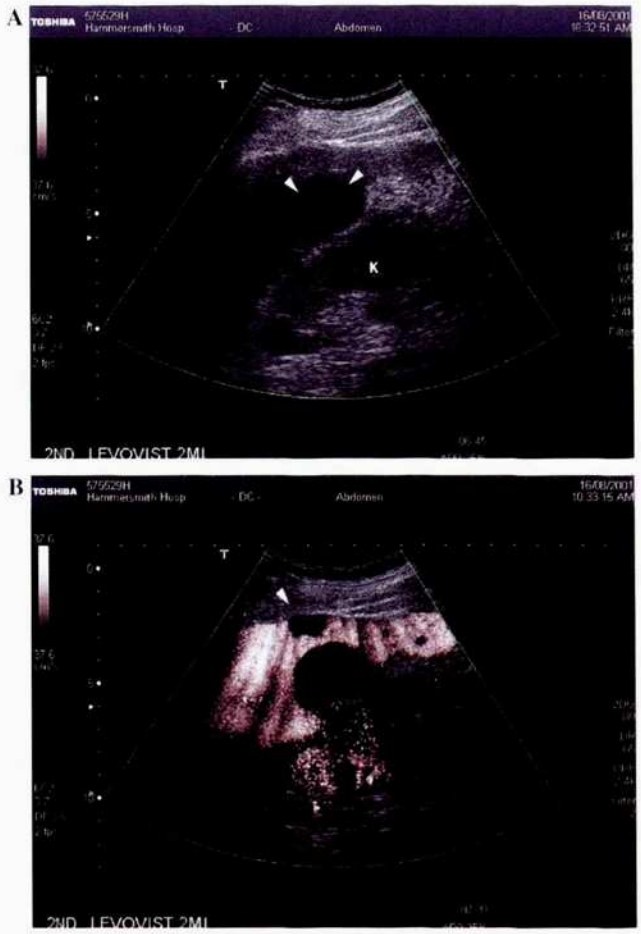



**Plate 9** Liver metastasis contrast study. (A) In this patient with a known colonic cancer, an obvious lesion compatible with a metastasis is seen in the inferior part of segment 5 (arrowheads); K, kidney. (B) In a registered image taken in the liver-specific phase after injection of the contrast agent Levovist (Schering, Berlin), using a liver-specific mode (Agent Detection Imaging) that shows the presence of contrast in color, this lesion is more clearly delineated, but an additional lesion that was not apparent before is also obvious (arrow).

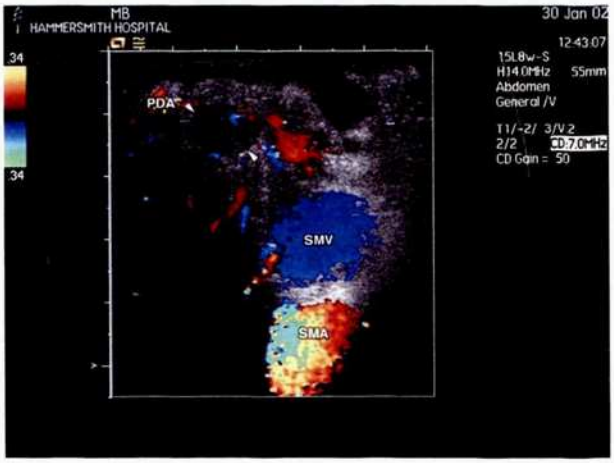



**Plate 11** Insulinoma intraoperative scan. This 7-mm insulinoma in the head of the pancreas could not be located in theater. The high-resolution scan obtained directly via the exposed pancreas clearly shows the lesion (arrowheads); the associated blood vessels are highlighted on color Doppler. PDA, Pancreatico-duodenal arcade; SMA, superior mesenteric artery; SMV, superior mesenteric vein.

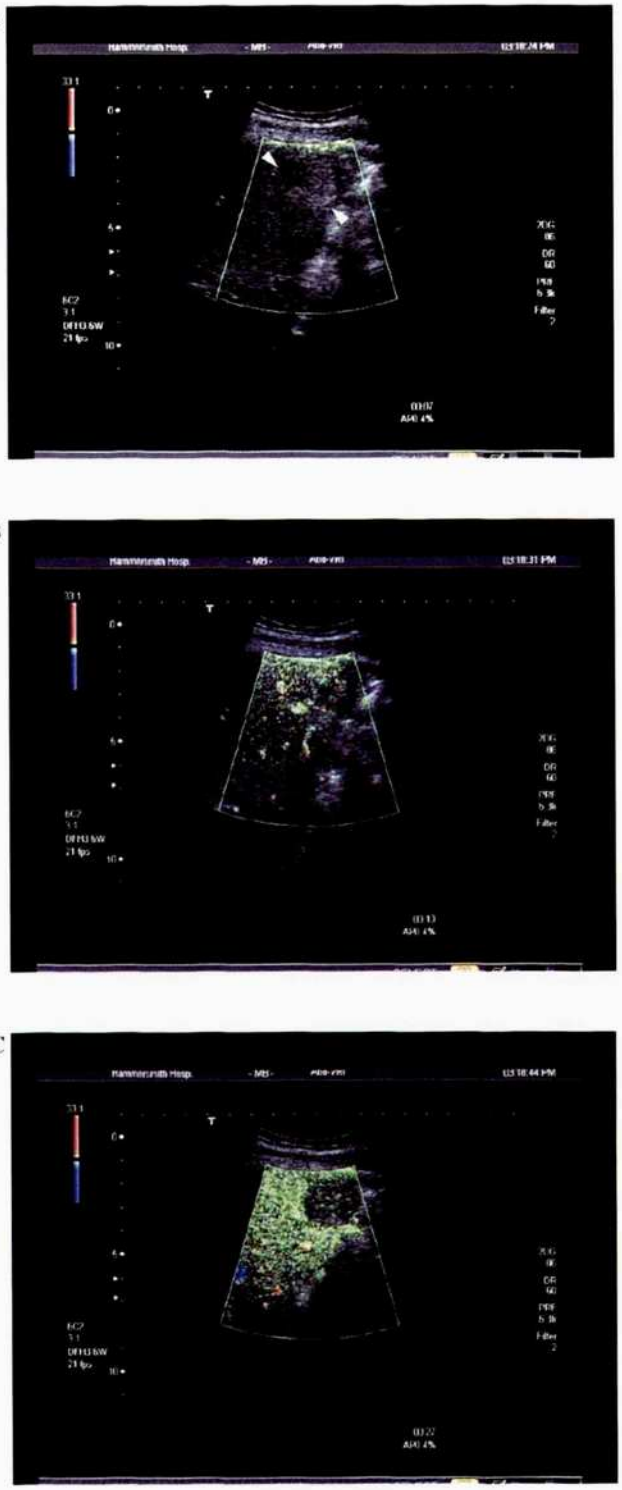



**Plate 10** Liver metastasis contrast study. (A) A metastasis from a colonic carcinoma is seen as an echogenic mass (arrowheads) at the beginning of an injection of a microbubble contrast agent, SonoVue (7 seconds postinjection). (B) In the next image from real-time sequence at 13 seconds postinjection (arterial phase), numerous small vessels enter the tumor from its periphery. In this microbubble-specific mode (Vascular Recognition Imaging, Toshiba, Tokyo), the contrast is depicted in green when it is stationary; the red and blue tints show moving microbubbles. (C) In the third frame, at 27 seconds, contrast is filling the liver parenchyma but the metastasis, with its low vascular volume, is highlighted as a signal void.

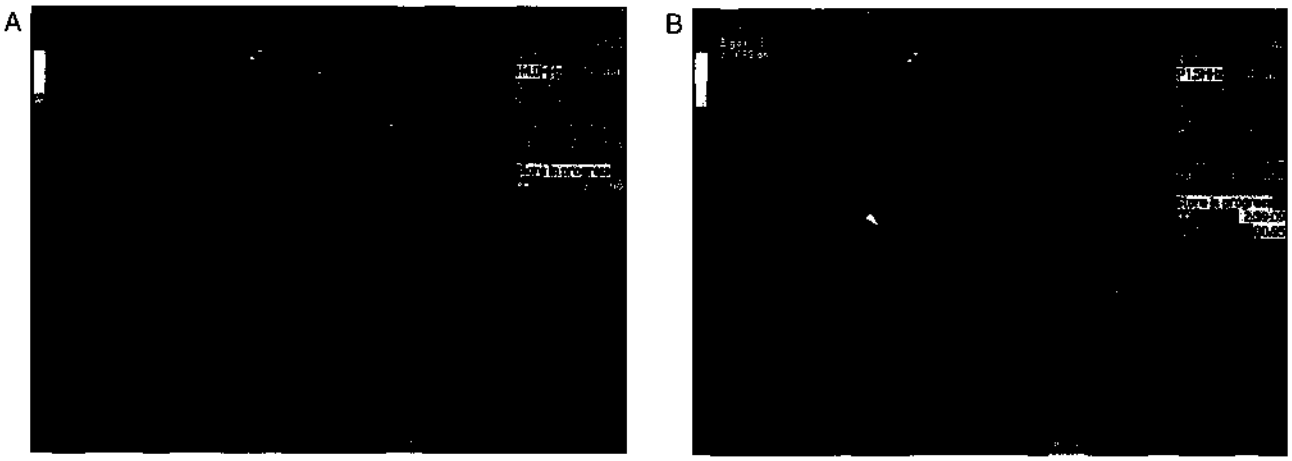



FIGURE 19 Stab wound of the liver. This patient suffered a penetrating injury to the right liver; despite knowing exactly where to look, it could not be demonstrated on grayscale ultrasound (A). Following administration of a contrast agent (SonoVue, Bracco, Milan), the lesion was clearly shown (arrowhead in B).

main pancreatic duct is seen as "tram lines" with a maximum caliber of 3 mm.

In acute pancreatitis, the gland swells, losing its normal shape, which has a waist at its neck, and becomes echo poor, but in practice, acute pancreatitis is a clinical diagnosis. An ultrasound scan should be obtained early in the course of the disease to look for gallstones. In chronic pancreatitis, there may be no changes on ultrasound until fibrosis and calcification supervene (Fig. 26). Dilatation and tortuosity of the main duct can be demonstrated.

Carcinoma of the pancreas produces a mass of variable echogenicity, often accompanied by duct dilatation and also by dilatation of the bile duct (the "double-duct sign") when, as is commonest, the tumor arises at the head of the pancreas (Fig. 27). Sometimes the diagnosis is obvious, with the mass perhaps involving the portal vein and lymphadenopathy, but often the features cannot be distinguished from focal pancreatitis. Endoscopic ultrasound offers some advantages but is, of course, more invasive.

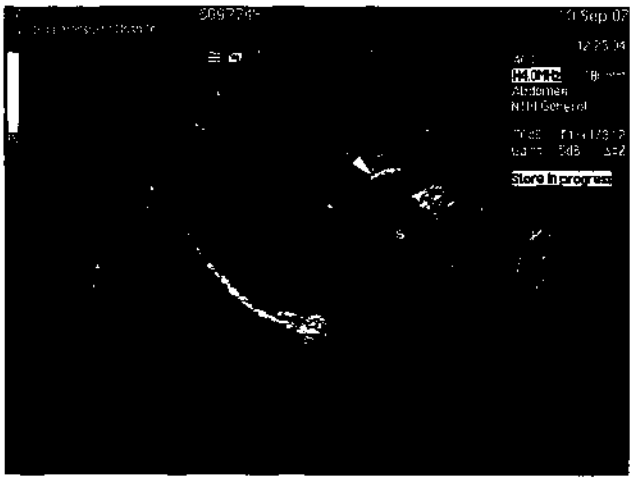


FIGURE 20 Gallstone. The strongly echogenic structure (arrowhead) in the gallbladder and its tell-tale shadowing (S) are diagnostic of a gallstone.

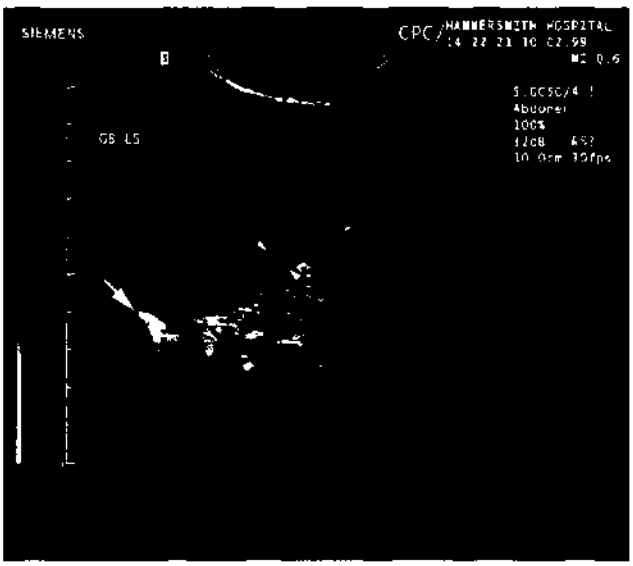



FIGURE 21 Acute cholecystitis. Wall thickening (arrowheads), often with splitting from edema, is typical in acute cholecystitis. There is usually local tenderness under the probe, which may be obvious in real time. The offending stone (arrow) is visible.

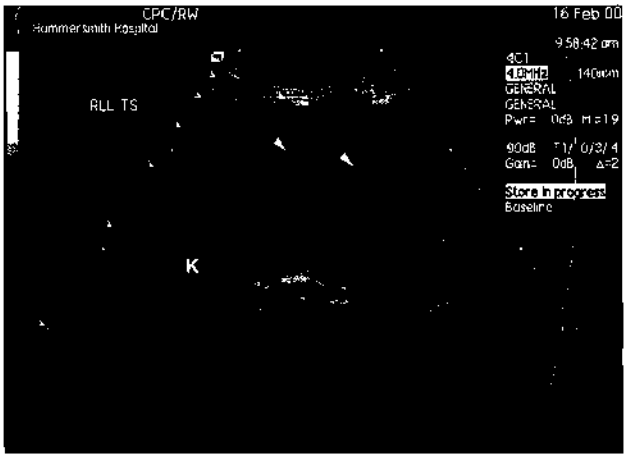



FIGURE 22 Carcinoma of the gallbladder. A large mass occupies the gallbladder fossa in this patient, who presented with jaundice. Embedded within the mass are several calculi (arrowheads). K, Kidney.

Of the rarer forms of pancreatic tumor, cystic carcinomas may produce a multicystic mass, though in the microcystic type the individual cysts are usually too small to be resolved and instead their numerous walls produce an echogenic mass. Papillary tumors are almost never visualized with ultrasound because they present at too small a size. Endocrine tumors are seen as echo-poor masses, but conventional scanning usually does not demonstrate hormonally active tumors because of their small size. However, the superior resolution of intraoperative scanning can reveal them and this is very useful to locate impalpable tumors (Fig. 28).

## NEW METHODS

The clinical impact of the advent of contrast agents for ultrasound has been described. Contrast agents also offer both anatomical information for delineating and characterizing focal lesions and functional information, derived by their use as tracers in tracking the transit of a bolus across a region of interest. In this role, they are supported by the small volumes required (0.5–5 ml is typical) and by the fact that new scanning modes are specific to the microbubbles, so that they can be almost completely separated from tissue signals and displayed as perfectly registered fusion images. In addition, they have a relatively short persistence after injection (2–10 minutes), so that repeat studies are feasible, and they are nontoxic. The fact that they can be selectively destroyed by acoustic pressures toward the top of the acceptable diagnostic range offers the unique opportunity for negative bolus studies that display the reperfusion of a tissue to give true hemodynamic information.

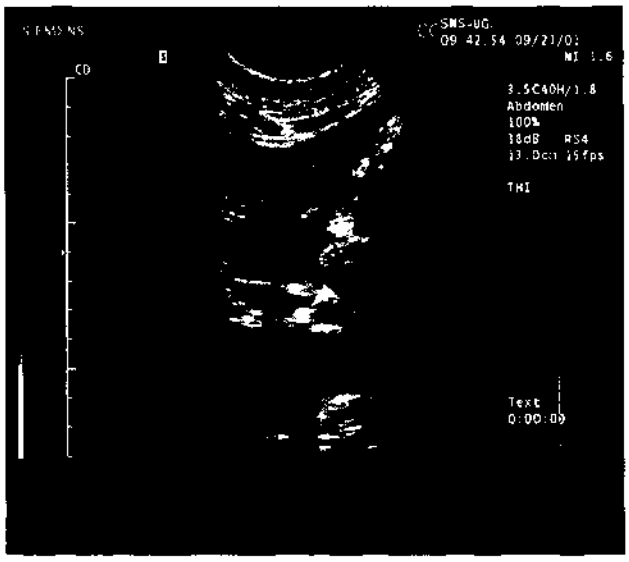



FIGURE 23 Stone in a dilated common bile duct. The echogenic structure within the dilated common bile duct (arrowhead) is identified as a stone by its shadowing. Dilatation is easily recognized on ultrasound, but stones are often much more elusive and endoscopic retrograde pancreatography may be required.

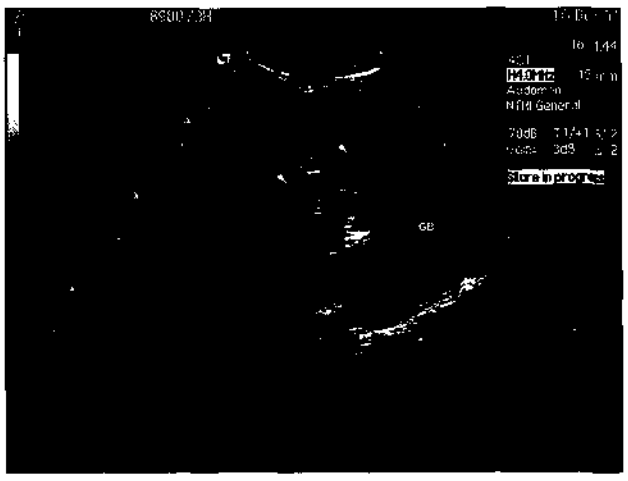



FIGURE 24 Dilated intrahepatic ducts. Normal ducts can just be resolved with ultrasound, but, when dilated, they are readily identified as tubes running alongside the vascular structures, producing a sort of duplicated anatomical pattern seen as "too many tubes" or the "parallel channel" signs of the ducts converging on the porta hepatis. GB, Gallbladder.

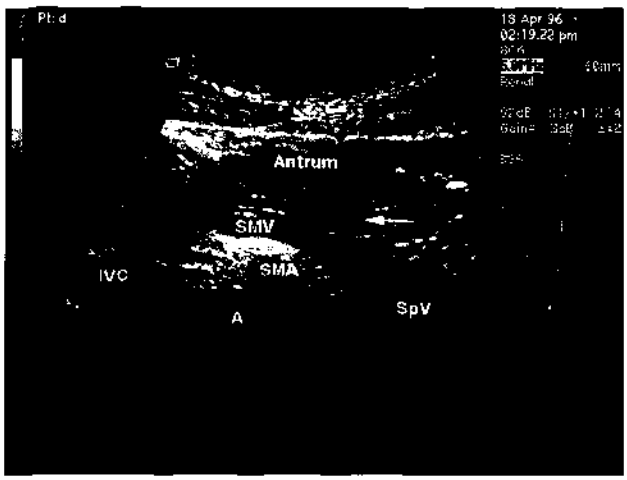



FIGURE 25 Pancreas. The proximal pancreas with its duct (arrow) lying across the superior mesenteric vessels is seen in this epigastric transverse section. A, Aorta; antrum, antrum of stomach; IVC, inferior vena cava; SMA, superior mesenteric artery; SMV, superior mesenteric vein; SpV, splenic vein.

A new way to use ultrasound (and other imaging) data that could prove to be important is elasticity imaging. For this, a series of images is collected while the tissue under study is distorted by applying gentle pressure, in order to move the tissue by about 5 mm. The images of the response to such a stress are used to form a strain image, which relates to the elastic (Young's) modulus; because this has several orders of magnitude greater range in human tissues than does the bulk modulus that is used for conventional ultrasound, the contrast between normal and pathological tissue is increased. In experimental situations, elastography can be implemented in real time and, for the liver, cardiac motion can be used as the stress. Although not ready for clinical use, this approach, which essentially images what the palpating hand discerns, is of great interest. Ultrasound can be implemented in three dimensions and this has proved useful when complex anatomy, such as the fetal face, needs to be depicted, to look for developmental abnormalities. In gastroenterology, this is probably of less importance, but the fact that three-dimensional images can be obtained in real time (so-called four-dimensional imaging) could be useful for interventional procedures in which it is important to visualize the needle path interactively in three dimensions.

## CONCLUSIONS

Developments in ultrasound have afforded it a unique role in the field of gastroenterology. It is the choice technique for the gallbladder and biliary tree, whereas Doppler gives unique information in portal hypertension and other vascular disorders of the liver. New techniques, especially with microbubble contrast agents, have made US comparable to helical CT for detecting and differentiating liver tumors and in abdominal trauma. The role of US is further extending to hollow abdominal organs, thanks to new technologies and systematic scanning approaches.


FIGURE 26 Chronic pancreatitis. Ultrasound is not sensitive to the changes of chronic pancreatitis, but when there is calcification, within the duct in this case (arrowheads), the changes are easily demonstrated. D, Pancreatic duct.

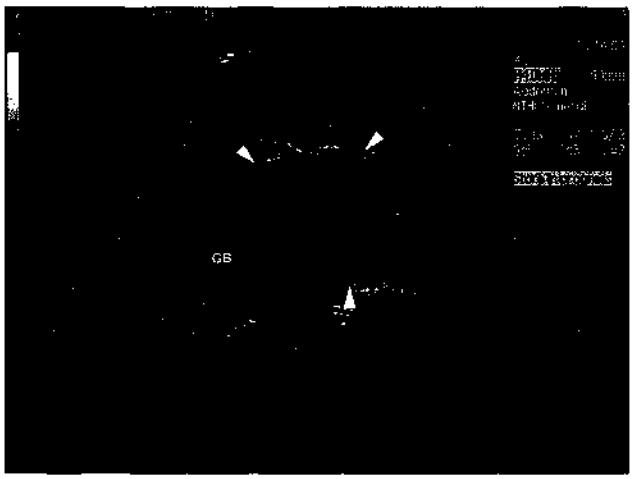



FIGURE 27 Carcinoma of the head of the pancreas. This large mass in the position of the head of the pancreas (arrowheads) proved to be a cancer, but the distinction from a chronic pancreatic mass is often impossible. Note the dilated gallbladder (GB).

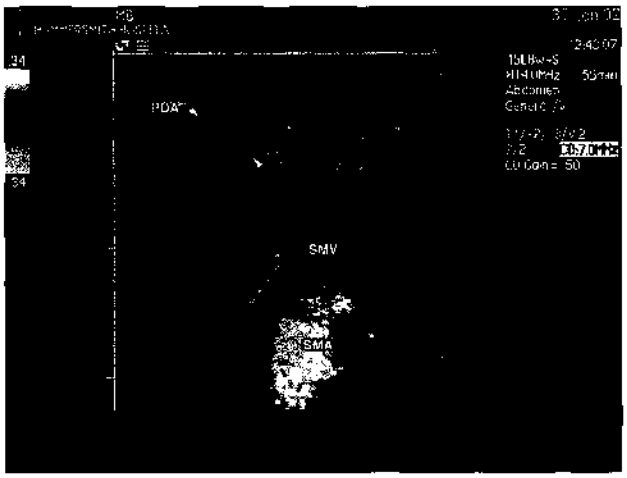



FIGURE 28 Insulinoma intraoperative scan. This 7-mm insulinoma in the head of the pancreas could not be located in theater. This high-resolution scan obtained directly via the exposed pancreas clearly shows the lesion (arrowheads); the associated blood vessels are highlighted on color Doppler. (See Plate 11.) PDA, Pancreatico-duodenal arcade; SMA, superior mesenteric artery; SMV, superior mesenteric vein.

## See Also the Following Articles

**Computed Tomography (CT) • Endoscopic Ultrasonography • Endoscopy, Complications of • Picture Archiving and Communication Systems (PACS) • Upper Gastrointestinal Endoscopy**

## Further Reading


Albrecht, T., and Blomley, M. J. (2001). Characteristics of hepatic hemangiomas at contrast-enhanced harmonic US. *Radiology* **220**, 269–270.

Bartolozzi, C., and Lencioni, R. (2001). Contrast-specific ultrasound imaging of focal liver lesions. Prologue to a promising future. *Eur. Radiol.* **11**(Suppl. 3), E13–E14.

Bartram, C. (2001). Radiologic evaluation of anorectal disorders. *Gastroenterol. Clin. North Am.* **30**, 55–75.

Bennett, G. L., and Hann, L. E. (2001). Pancreatic ultrasonography. *Surg. Clin. North Am.* **81**, 259–281.

Brand, R. (2001). The diagnosis of pancreatic cancer. *Cancer J.* **7**, 287–297.

Damore, L. J., 2nd, Cook, C. H., *et al.* (2001). Ultrasonography incorrectly diagnoses gallbladder polyps. *Surg. Laparosc. Endosc. Percutan. Tech.* **11**, 88–91.

Freeny, P. C. (2001). Pancreatic carcinoma: Imaging update 2001. *Dig. Dis.* **19**, 37–46.

Gaiani, S., Volpe, L., *et al.* (2001). Vascularity of liver tumours and recent advances in doppler ultrasound. *J. Hepatol.* **34**, 474–482.

Giorgio, A., Tarantino, L., *et al.* (2001). Hydatid liver cyst: An 11-year experience of treatment with percutaneous aspiration and ethanol injection. *J. Ultrasound. Med.* **20**, 729–738.

Hunt, G. C., and Faigel, D. O. (2002). Assessment of EUS for diagnosing, staging, and determining resectability of pancreatic cancer: A review. *Gastrointest. Endosc.* **55**, 232–237.

Kalimi, R., Geceller, G. R., *et al.* (2001). Diagnosis of acute cholecystitis: Sensitivity of sonography, cholescintigraphy, and combined sonography–cholescintigraphy. *J. Am. Coll. Surg.* **193**, 609–613.

Li, P. C., and Wu, C. L. (2001). Strain compounding: Spatial resolution and performance on human images. *Ultrasound Med. Biol.* **27**, 1535–1541.

Martinez-Noguera, A., Montserrat, E., *et al.* (2001). Ultrasound of the pancreas: Update and controversies. *Eur. Radiol.* **11**, 1594–1606.

Mirilas, P., Koumanidou, C., *et al.* (2001). Sonographic features indicative of hydrostatic reducibility of intestinal intussusception in infancy and early childhood. *Eur. Radiol.* **11**, 2576–2580.

Mortele, K. J., and Ros, P. R. (2001). Imaging of diffuse liver disease. *Semin. Liver Dis.* **21**, 195–212.

Roberts, S. A. (2002). Laparoscopic ultrasound staging of upper gastrointestinal tract tumors: Is it really necessary? *Abdom. Imaging* **27**, 1–5.

Shorvon, P. (2002). Imaging of appendicitis: A cautionary note. *Br. J. Radiol.* **75**, 717–720.

Sofia, S., Casali, A., *et al.* (2001). Sonographic diagnosis of adult intussusception. *Abdom. Imaging* **26**, 483–486.

Tandon, M., and Topazian, M. (2001). Endoscopic ultrasound in idiopathic acute pancreatitis. *Am. J. Gastroenterol.* **96**, 705–709.

Wilson, S. R., and Burns, P. N. (2001). Liver mass evaluation with ultrasound: The impact of microbubble contrast agents and pulse inversion imaging. *Semin. Liver Dis.* **21**, 147–159.

Wilson, S. R., Burns, P. N., *et al.* (2000). Harmonic hepatic US with microbubble contrast agent: Initial experience showing improved characterization of hemangioma, hepatocellular carcinoma, and metastasis. *Radiology* **215**, 153–161.

Yarmenitis, S. D. (2002). Ultrasound of the gallbladder and the biliary tree. *Eur. Radiol.* **12**, 270–282.

# Upper Gastrointestinal Bleeding

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**hematemesis** Vomiting of blood.
**hematochezia** Passage of bright red or wine-colored stool, usually representing bleeding from the lower gastrointestinal tract, often the colon.
**melena** Passage of dark black stool, representing blood typically from an upper gastrointestinal source.
**upper gastrointestinal bleeding** Loss of blood from the gastrointestinal tract proximal to the ligament of Treitz.

**Acute upper gastrointestinal bleeding is a common medical condition encountered by generalists and specialists alike. Despite the significant strides in the development of effective endoscopic techniques for hemostasis, this type of bleeding, especially in the elderly, remains a significant cause of morbidity and potential mortality. Prompt recognition of the patient with acute upper gastrointestinal bleeding will ensure timely endoscopic evaluation, which will provide not only a diagnosis but also the opportunity for endoscopic therapy and triage. Patients with low-risk lesions at endoscopy can be managed with earlier hospital discharge, assuming there is no significant comorbidity.**

## INTRODUCTION

Current estimates of the incidence of hospitalization for acute upper gastrointestinal bleeding (UGIB) in the United States population range from 30 to 100 per 100,000, which translates to approximately 400,000 hospital admissions yearly in the United States. Whether the widespread adoption of *Helicobacter pylori* eradication therapy for patients with dyspepsia and peptic ulcer as well as the use of safer nonsteroidal antiinflammatory drugs (NSAIDs) will reduce this number remains to be explored. These incidence data do not account for those patients who experience acute UGIB while hospitalized; given the narrower differential diagnosis and higher mortality, such patients represent a unique subset of bleeders.

## ETIOLOGY

The most common cause of acute UGIB remains peptic ulcer disease (Fig. 1). Gastroesophageal varices, Mallory–Weiss tears, and acute gastric mucosal lesions (erosions) are the next most frequent etiologies. It is important to recognize that the most common cause identified in a particular study is dependent on the population examined. For example, peptic ulcer and acute gastric mucosal lesions represent the most common causes in NSAID users, whereas variceal bleeding is most prevalent in patients with portal hypertension and cirrhosis.

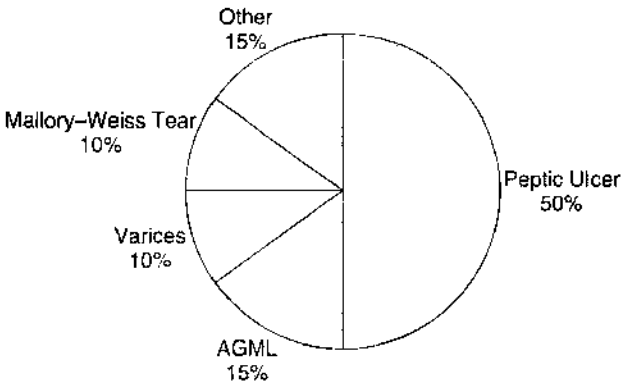


**FIGURE 1** Etiology of upper GI bleeding. AGML, Acute gastric mucosal lesion.

## APPROACH TO THE PATIENT

The first step in the management of the patient with UGIB is prompt diagnosis. Although most patients manifest with an alteration in stool color, usually melena associated with hematemesis, the initial presentation in some patients will be hematochezia alone, which may suggest a lower gastrointestinal (GI) bleeding source. The color of both vomitus and stool not only points to the site of bleeding (upper versus lower GI tract), but also provides important prognostic information. Patients who present with hematemesis and melena generally have more substantial blood loss as compared to patients who present with "coffee-ground" hematemesis and brown stool or melena without hematemesis. Red hematemesis also suggests more acute and significant

 

blood loss and is associated with a worse prognosis compared to a presentation with coffee-ground hematemesis alone. Generally, the more significant the blood loss, the more likely the bleeding source is arterial.

A thorough history often provides important clues to the underlying cause of bleeding. A thorough systematic review for diseases of the esophagus, stomach, and duodenum should be performed. Rarely, nasopharyngeal and oropharyngeal bleeding will masquerade as UGIB in the absence of symptoms pointing to this possibility. The presence of dysphagia or reflux symptoms may suggest esophageal cancer and gastroesophageal reflux disease, respectively. Because NSAID use is so prevalent in patients with gastric and duodenal ulcer disease and acute mucosal lesions, it is important to question specifically not only regarding prescription use but also the use of over-the-counter NSAIDs, because many patients do not consider these "medications." The dose and duration are also important to ascertain, because high-dose NSAID use of long duration is more likely to produce peptic ulcer as compared to very short-term intermittent use. A past history of peptic ulcer, particularly bleeding ulcer, is important to identify. Associated symptoms of ulcer include nausea, vomiting, and nocturnal epigastric distress. Nevertheless, the absence of abdominal pain is common in peptic ulcer regardless of NSAID use. Painless bleeding is also more common in patients with mucosal disease such as vascular ectasias. Vascular ectasias are most prevalent in the elderly and in those with underlying renal disease, typically elderly patients on dialysis. Approximately one-third of patients with Mallory–Weiss tear will not present with a classic history of repetitive retching followed by hematemesis. Portal hypertension may be suggested in the patient with established chronic hepatitis or significant alcohol use associated with stigmata of chronic liver disease. A history of aortic aneurysm or prior repair should raise the possibility of an aortoenteric fistula, which would require not only endoscopy but also computed tomography to diagnose.

Following recognition and diagnosis, initial evaluation must promptly address hemodynamic status. Persistent bleeding with subsequent volume loss, if left untreated, will lead to multiorgan failure and death caused by hypoperfusion. Initial hemodynamic assessment should use vital signs as a measure of volume status. Resting tachycardia and orthostatic hypotension represent a $>15\%$ volume loss. The degree of resuscitation with normal saline and/or blood products should be dictated by the volume status (vital signs), initial hematocrit, and evidence of ongoing blood loss as assessed clinically (recurrent/persistent hematemesis, melena, etc.). Careful administration of blood products and fluids should be provided for the elderly patients, especially those with underlying heart disease or renal dysfunction. Maintaining a hematocrit above 30% is appropriate for those with underlying coronary artery disease to maximize oxygen delivery. It is critical to remember that the hematocrit can be influenced by the degree of volume resuscitation and prior volume status. Therefore, the hematocrit must be interpreted in the context of these other factors. Determination of platelet count and prothrombin time is important, and is mandatory for those receiving medications such as coumadin. In addition, an elevation of prothrombin time and/or thrombocytopenia could point to underlying portal hypertension. Elevation of blood urea nitrogen concentration can be observed with both upper and lower GI bleeding, although this is typically higher with UGIB. Patients at risk for coronary disease should have an electrocardiogram to exclude myocardial ischemia; occult ischemia and infarction have been found in 10% or more of elderly patients. Chest radiography should be used selectively.

The site of gastrointestinal blood loss is generally apparent based on the history or witnessing of hematemesis or melena. When the diagnosis of UGIB is in doubt, nasogastric (NG) aspiration should be considered. Identification of bile in the aspirate suggests either bleeding distal to the duodenum or bleeding that has stopped. Conversely, if no bile is found, bleeding may still be present in the duodenum. Although melena almost uniformly represents bleeding proximal to the colon, in elderly patients with hematochezia in the absence of hematemesis, documentation of an upper gastrointestinal source is critical. When there is active gastrointestinal blood loss (unstable vital signs) and hematochezia, urgent upper endoscopy should be performed when bile is not found on NG aspirate, because a duodenal ulcer could be present. When the patient presents with hematemesis or gross melena with stable vitals signs, NG aspiration is not mandatory, because the site of bleeding is known. If there is concern about active bleeding, which may influence the timing of endoscopy, NG aspiration to sample for fresh blood is reasonable. Routine use of nasogastric lavage prior to upper endoscopy is unnecessary, because standard NG tubes cannot adequately clear the stomach of blood and clots; a large-bore tube (Edlich tube) is required in this setting. Generally, even with active bleeding and blood clots in the stomach, the bleeding source can be accurately identified and endoscopically treated at the time of endoscopy.

## RISK ASSESSMENT

When initially evaluating the patient, outcome is intuitively assessed. For example, it is recognized that the major risk factor impacting the outcome of UGIB is uncontrolled and/or recurrent hemorrhage. Both clinical and endoscopic features help predict recurrent hemorrhage and poor outcome. Identification of these patients is how early endoscopic examination and endoscopic therapy will have the most beneficial impact.

A number of clinical factors have been examined for their predictive value for risk of recurrent hemorrhage. These include age greater than 65 years, gender, alcohol or tobacco use, preexisting liver disease, renal disease, vascular malformations, anticoagulant use, unstable vital signs (tachycardia, orthostasis, shock), ongoing bleeding (hemoglobin $<9$ g/dl), and blood urea nitrogen (BUN) concentration $>90$ mg/dl. However, when controlling for these variables, independent predictors include unstable vital signs (tachycardia, orthostasis, shock) and clinical evidence of ongoing blood loss. When combining these factors in a scoring system, more than 90% of patients who require intervention can be identified, which generally will include endoscopic therapy. Conversely, it is now recognized that patients without these clinical features are at low risk for recurrent bleeding and may be managed with less urgency.

All patients with gastrointestinal bleeding require neither intensive care unit (ICU) stay nor even hospital admission. Factors that may prompt admission for ICU monitoring include active bleeding, hypotension, coagulopathy, altered mental status, and comorbid conditions, especially in elderly patients. Nevertheless, clinical judgment should guide the need for observation in an intensive care unit. Emerging data suggest that clinical features alone may predict which patients require hospitalization for bleeding.

Most studies have combined both clinical and endoscopic features to assess risk for recurrent bleeding, poor outcome, and need for hospitalization. Rockhall and colleagues developed one of the best-studied scoring systems. This investigation found that age, vital signs, comorbidity, source of hemorrhage, and endoscopic stigmata could be used to classify low risk and thus eligibility for outpatient care. In this study, patients without these features had no mortality at short-term followup. Other investigators have used similar combinations of clinical and endoscopic features to show that early discharge or even discharge following endoscopy is both safe and cost effective. One study used well-defined criteria for low-risk discharged patients meeting these criteria after endoscopy in the emergency room. Followup demonstrated a low risk for recurrent bleeding (less than 5%) with 0% mortality.

TABLE 1 Prevalence and Outcome of Stigmata of Hemorrhage in Bleeding Ulcers

| Endoscopic stigmata | Prevalence (%) | Rebleeding rate (%) |
|---|---|---|
| Spurting | 10 | 80 |
| Visible vessel | 20 | 50 |
| Clot | 20 | 15 |
| Flat spots | 15 | 5 |
| Clean base | 30 | 5 |

Endoscopic features have been well established as predictors for recurrent gastrointestinal bleeding. These features have primarily been studied in peptic ulcer hemorrhage but are likely applicable to other nonvariceal causes. Although studies have suggested that large ulcers, ulcers high on the lesser curvature, and posterior duodenal ulcers have the highest risk of rebleeding, it is now recognized that endoscopic features of the lesion—so-called stigmata of hemorrhage—are the most important (Table 1; Figs. 2–6). These stigmata have been repeatedly shown to predict accurately the risk of recurrent bleeding, the need for surgery, and mortality. The rebleeding rate for clots overlying an ulcer is variable among studies, and these differences are likely related to the fact that the blood clot may obscure underlying stigmata such as a visible vessel.

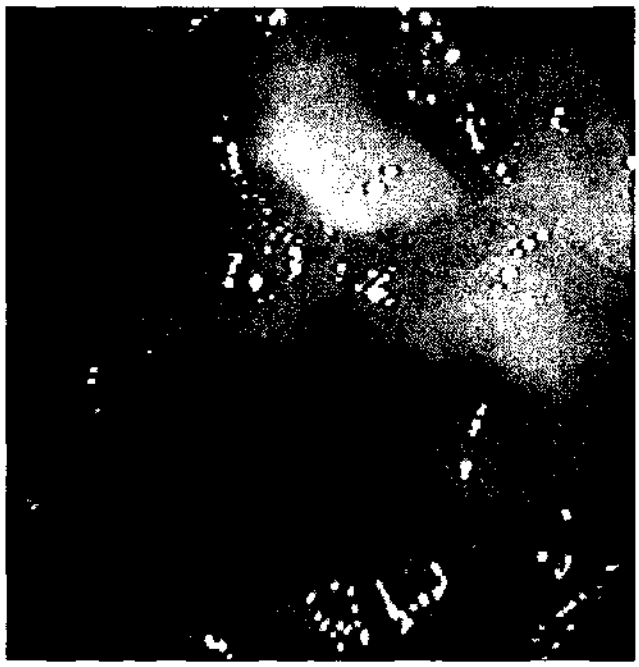

FIGURE 2 Clean-based ulcer in the peripyloric area.

FIGURE 3 Linear ulcer in the gastric body; note flat black spots.

Over the past several decades, despite the efficacy of endoscopic therapy, the mortality rate for UGIB has remained relatively stable at approximately 5–10%. It is felt that this rate has not fallen because elderly patients, who are more likely to die, comprise a larger proportion of the bleeding population. It is recognized that age greater than 60 years increases the risk of death for UGIB by approximately 10-fold. Patients who have substantial bleeding while hospitalized have mortality rates of approximately 30%, likely due to the significant comorbidity requiring hospitalization. Regardless of the group, patients with UGIB rarely die from blood loss, but rather bleeding exacerbates any underlying comorbidities.

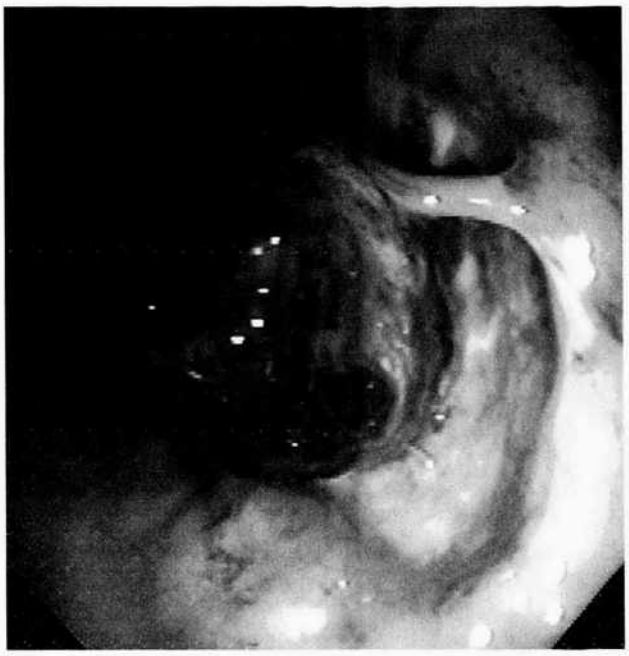

FIGURE 4 Large clot overlying a deep ulcer on the lesser curvature.

In summary, current evidence strongly supports the use of both clinical and endoscopic features to predict recurrent bleeding and outcome. When these features are combined, it is possible to determine not only if patients require more careful monitoring such as in an ICU, but also if patients require hospital admission.

## ENDOSCOPIC HEMOSTASIS

A randomized trial of 100 patients with UGIB comparing routine endoscopy to upper gastrointestinal barium study in 1981 showed no difference in hospital stay, rebleeding rate, and mortality. This result is not surprising given the fact that, at that time, endoscopy represented a diagnostic tool alone. Subsequently, Laine prospectively randomized patients with bleeding peptic ulcers and high-risk stigmata to endoscopic therapy using a thermal probe or sham endoscopic therapy. This study demonstrated an improved outcome in the treated group with greater hemostasis (90% of treated patients compared to 13%), lower transfusion requirements, less urgent surgery, and a shorter hospital stay. Mortality was unchanged, perhaps because death is an

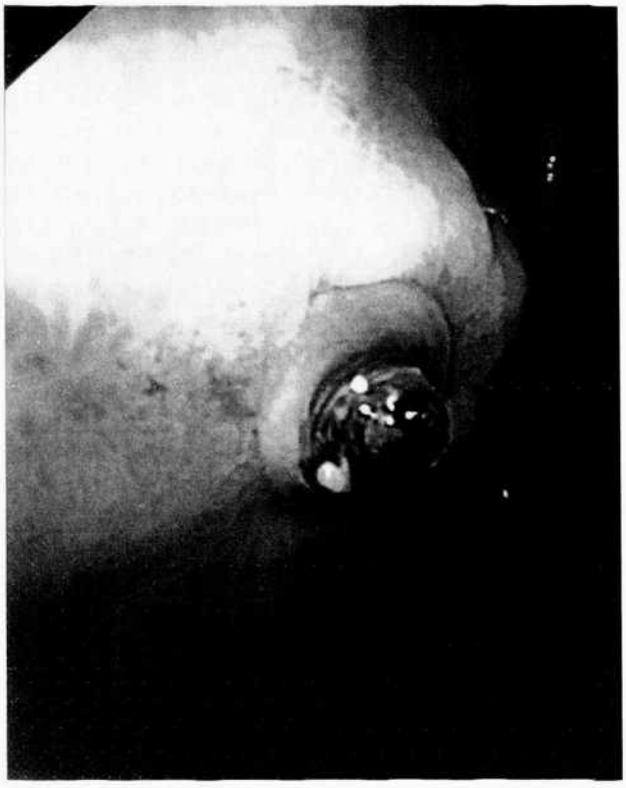

FIGURE 5 Nipplelike projection (visible vessel) from a small ulcer in the gastric body.

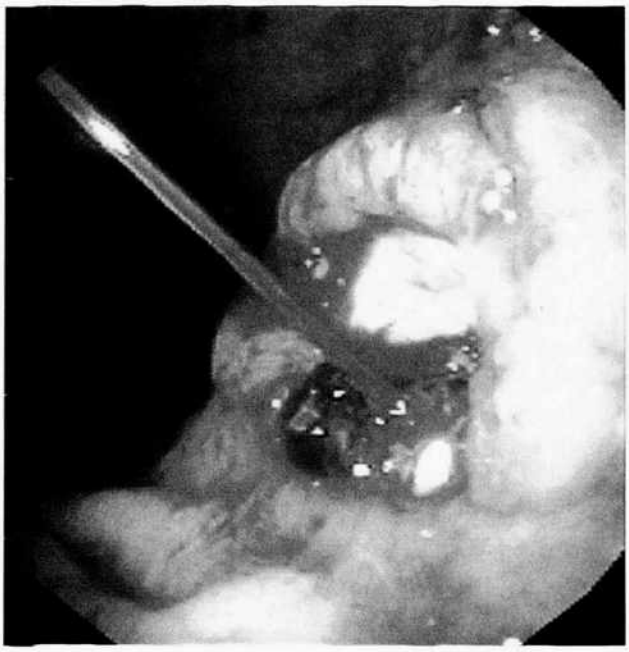

FIGURE 6 Small ulcer in the gastric body; note active arterial spurting.

uncommon event in UGIB. Since this seminal study was undertaken, numerous trials evaluating peptic ulcer, Mallory–Weiss tear, and esophageal variceal bleeding have shown the efficacy of endoscopic therapy in controlling bleeding, reducing the need for emergent surgery, and preventing rebleeding. Using meta-analysis, Cook and colleagues also showed that not only will endoscopic therapy decrease rebleeding, but also mortality in bleeding peptic ulcers.

## Endoscopic Hemostatic Methods

A variety of endoscopic techniques have been developed and tested for the control of gastrointestinal bleeding, principally from peptic ulcer. Broadly, these can be categorized as thermal, injection, and mechanical techniques. The most widely tested and currently utilized techniques are the thermal methods. A 7 or 10 French probe placed through the endoscope channel delivering heat energy to the bleeding point has been found to be highly effective. One probe uses electrical energy to deliver heat at over 200°F to the tip of the probe (heater probe). The other method uses bipolar current that passes through the tip of the probe to generate heat. Thermal methods deliver heat to the bleeding vessel, which seals the defect in the arterial wall (coaptive coagulation), thus controlling active bleeding and preventing rebleeding. The depth of tissue injury for these thermal methods is shallow and thus perforation is rare. Noncontact devices include the argon and neodymium : yttrium aluminum garnet (Nd : YAG) crystal laser. Although effective, the YAG laser has fallen out of favor because of its cost, difficult and cumbersome use, and higher perforation rate. More recently, argon plasma coagulation has been utilized and is effective to ablate superficial lesions such as vascular ectasias (Fig. 7). This device works by passing Argon gas from the end of the probe, which becomes ignited, resulting in superficial tissue coagulation. Depending on the power setting, the depth of injury is also shallow and risk of perforation very small.

The technique of injection therapy is widely available, easy to perform, and efficacious. A variety of agents have been used, most frequently a dilute concentration (1:10,000) of epinephrine. It is felt that epinephrine results in both vasoconstriction and vessel occlusion (tamponade) by the fluid bolus. Injection of saline alone, however, does not appear as effective as epinephrine. Other tested agents include those causing tissue necrosis or fixation (ethanol, polidocanol, sodium tetradecylsulfate, ethanolamine) and clot formation (thrombin). Using a standard sclerotherapy needle, the technique involves injection of aliquots of 1–2 ml of dilute epinephrine (maximum 20 ml), or 0.1–0.2 ml (total volume 2 ml) of these sclerosing agents, because the sclerosing agents result in greater tissue injury and have a higher perforation rate. One large trial found thrombin to be effective and to have a low complication rate. This was given in doses of 61,000 international units (IU). Injection of cyanoacrylate glue, which is not available in the United States, has been used in

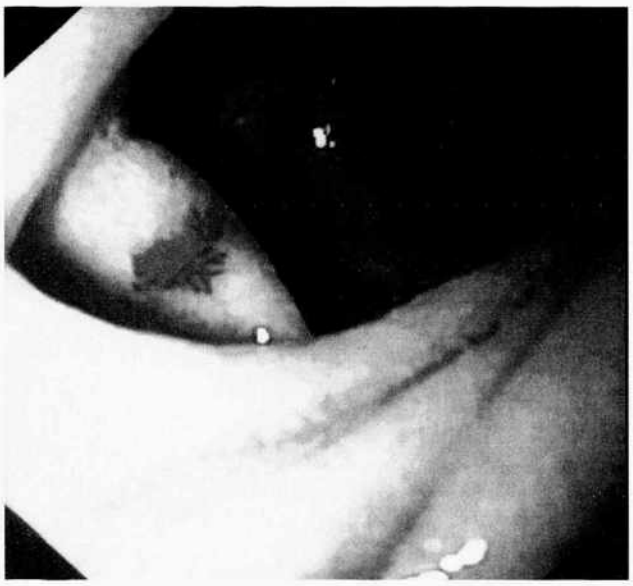

FIGURE 7 Small spiderweb-like lesion in the second duodenum, typical for a vascular ectasia.

European trials, but multiple endoscopy sessions may be required.

The most common mechanical technique employed is the endoscopic mucosal clip (hemoclip). Although best tested for use in peptic ulcer bleeding, these clips can also be used for Mallory–Weiss tears. One recent trial comparing a heater probe to a clipping device suggested superior efficacy for clips. Nevertheless, in the United States, thermal and injection therapies remain the standard of care.

## EFFICACY OF ENDOSCOPY THERAPY

Numerous trials have compared each of these therapies either to placebo (medication), other endoscopic techniques, or in combination. Generally, endoscopic therapy is administered to patients with actively bleeding ulcers or with high-risk stigmata, including visible vessels. Although not as widely studied, these therapies are effective for other mucosal lesions, including esophageal ulcers and Mallory–Weiss tears. Generally, these techniques have been shown to reduce the rate of recurrent bleeding to less than 20%, although a substantial effect on mortality has rarely been shown. Several trials have used combination therapy with epinephrine injection followed by thermal therapy and suggest superiority of the combination method.

## MANAGEMENT OF ACUTE VARICEAL BLEEDING

Prompt recognition of the patient at risk for portal hypertension-related bleeding is critical because of the higher morbidity and mortality of these patients, coupled with the fact that specific endoscopic therapy is required and selected pharmacological therapies are beneficial. Approximately 35–80% of patients with cirrhosis may develop varices, usually esophageal, with a much smaller percentage developing gastric varices. The patient who should be considered at risk for variceal bleeding is one who presents with stigmata of chronic liver disease (jaundice, cutaneous stigmata of chronic liver disease, ascites). Additional laboratory clues may include hypoprothrombinemia, thrombocytopenia, jaundice, and hypoalbuminemia. In the patient considered at risk by history, physical examination, and laboratory studies, pharmacologic therapy can be initiated prior to endoscopic therapy with octreotide, a synthetic long-acting analogue of somatostatin. This agent has essentially replaced the combination of vasopressin and nitrates, given their higher complications as well as superior efficacy of octreotide. Endoscopic therapy for esophageal varices includes sclerotherapy or, more recently, esophageal banding. This latter technique involves the endoscopic delivery of ringlike elastic bands that are placed directly on varices. Trials comparing sclerotherapy to variceal banding have shown improved efficacy in preventing rebleeding as well as a reduction in complication rates with banding. Active bleeding from gastric varices can be treated endoscopically, although this is not a long-term option and surgical therapy or transjugular intrahepatic portosystemic shunt (TIPS) therapy will be required. Transplantation is another potential option in the appropriate candidate. For the patient with acute variceal bleeding, antibiotic prophylaxis with a quinolone for 7 days has also been recommended because this decreases overall infection rates, including spontaneous bacterial peritonitis.

## RECURRENT BLEEDING

Despite the efficacy of endoscopic therapies, bleeding still recurs in 15–20% of patients (range 5–35%) treated endoscopically with spurting vessels, and bleeding and nonbleeding visible vessels. Rebleeding from esophageal varices also remains a problem, although less so since the introduction of banding. The mortality in these groups remains substantial at 10% or greater. Patients with rebleeding can be treated with repeat endoscopic therapy, angiographic embolization, or surgery.

### Repeat Endoscopic Therapy

There has been one prospective randomized trial comparing repeat endoscopic therapy to surgery for patients rebleeding from peptic ulcer. Repeat endoscopic therapy was successful in 73% of patients, and the overall complication rate was twice as high in the surgery group. Nevertheless, length of hospital stay, transfusion requirements, and mortality were no different. Given the data from this well-done study, an attempt at repeat endoscopic therapy should be performed prior to surgical therapy for patients with ulcer-related rebleeding. Although not studied, it is likely that other nonvariceal causes of rebleeding can be similarly managed, such as Mallory–Weiss tear. In the high-risk bleeder, some have performed "second look" endoscopies in the hopes of retreating endoscopically persistent high-risk lesions, thereby reducing recurrent bleeding. The data for this have been mixed and no firm recommendation can be made.

### Angiographic Therapy

Angiography can be used initially in the patient with UGIB to identify the site of bleeding when endoscopy

cannot be performed or when the bleeding source cannot be identified due to massive bleeding. To demonstrate extravasation, active bleeding at approximately 1 ml/minute must be present. If active arterial bleeding is identified, selective placement of coils or foam pledgets into the artery is performed. When the site of bleeding is known but bleeding is intermittent, empiric embolization of the appropriate arterial source is an option. In the past, selective infusion of arterial vasopressin was utilized. However, the systemic effects of widespread vasoconstriction may be complicated by myocardial infarction and arrhythmias. The success of embolization is approximately 80%, with a low complication rate, including perforation.

### Surgical Therapy

Many studies have shown that surgery is required for recurrent bleeding in approximately 5–10% of patients with ulcer-related bleeding. The precise timing of surgery for patients with recurrent bleeding is not well established. Although successful in halting bleeding, the complication rate with surgery is high and mortality rates of over 20% have been reported. Unfortunately, it is often the elderly patients with comorbidity who fail endoscopic therapy, and they are poor surgical candidates. The type of surgery undertaken will depend on the location of the lesion and the experience of the surgeon. Generally, in the high-risk patient, angiographic embolization can be attempted first; if unsuccessful, surgical therapy can then be undertaken.

### Medical Therapy

Although antacid therapy has been routinely prescribed for UGIB for many years, large trials of over 1000 patients have failed to demonstrate efficacy of histamine-2 (H2) receptor blockers over placebo. A large meta-analysis did suggest a decrease in surgery and death, however. Despite these discouraging results with these agents, antacid therapy has some scientific rationale. *In vitro*, the combination of blood and acid at a pH less than 5 results in coagulopathy, with reduction in platelet aggregation and fibrin formation. These abnormalities were not seen when the pH was greater than 6.

With the availability of potent acid-suppressing agents (proton pump inhibitors), enthusiasm for acid reduction in the setting of bleeding has been rekindled. These agents could theoretically be effective, given their efficacy is raising gastric pH. Several studies from Europe have shown that a continuous infusion of omeprazole in bleeding peptic ulcer decreases rebleeding rates. The use of high-dose oral therapy was shown to be effective in one study, and there appears to be additional efficacy for the use of omeprazole following endoscopic therapy.

Although widely used for the therapy of variceal hemorrhage, some data suggest that intravenous somatostatin and octreotide also have benefit for ulcer-related bleeding. A recent meta-analysis suggested a reduction in continued or recurrent bleeding; however, given the efficacy of endoscopic therapies, perhaps combined with oral omeprazole, these agents should rarely be given.

## POSTTHERAPY FOLLOWUP

### Immediate

Assuming endoscopic therapy has been performed successfully or the patient does not require endoscopic therapy at the time of endoscopy, the intensity of subsequent monitoring for rebleeding is dependent on the likelihood of rebleeding and the overall health status of the patient. Elderly patients with comorbidity with ulcer-related bleeding requiring endoscopic hemostasis may require additional ICU observation, whereas a younger healthy patient with a Mallory–Weiss tear treated endoscopically could be managed on a ward and considered for early discharge (within 24 hours of endoscopy). Monitoring should include not only frequent vital signs and hematocrit, but also a careful recording of stool frequency and color as important clues to recurrent bleeding. Generally, ulcer-related rebleeding occurs approximately 24–72 hours after initial stabilization. For the patient considered at low risk for recurrent bleeding, the diet can be liberalized and early discharge planned, assuming there is adequate home support. If repeat endoscopy is either planned or felt likely because of high-risk stigmata, a completely liquid diet is appropriate for the first 24 hours after endoscopic therapy. Hospital discharge is appropriate 48–72 hours after endoscopic therapy in the elderly patient.

### Curing the Ulcer Disease

Prior to awareness of the role of *H. pylori* in the pathogenesis of peptic ulcer, long-term strategies following ulcer hemorrhage consisted of maintenance antacid therapy to prevent recurrent ulceration and thus bleeding. In a study by Jensen and colleagues, the use of maintenance ranitidine (150 mg/day) decreased the recurrence rate of duodenal ulcer bleeding over 1 year from 36 to 9%. Given their additional potency, it is likely that long-term therapy with proton pump inhibitor therapy would be even more effective. No differences

have been shown in ulcer healing between bleeding and nonbleeding ulcers.

Determination of *H. pylori* status during the hospitalization is mandatory for patients with bleeding ulcer. Biopsy of the gastric antrum for urease testing [with a kit using the *Campylobacter*-like organism (CLO) test] can be performed at the time of endoscopy, although the sensitivity has been found to be less in this setting, perhaps due to interference from blood. Random biopsies can be obtained for gastric histology, particularly if neoplasm needs to be excluded and assessment for *H. pylori* performed. Stool antigen tests are another alternative. To ensure an accurate diagnosis, combination testing with more than one method is suggested. Numerous studies have now demonstrated that successful eradication of *H. pylori* effectively cures peptic ulcer disease. For patients with bleeding ulcer, this is translated into decreased ulcer and hemorrhage risk. Indeed, most studies suggest that the bleeding rate following successful eradication is less than 5%. Given this striking success, it is critical to verify the eradication of *H. pylori* either with a urea breath test, repeat endoscopy and biopsy, or stool antigen testing. If *H. pylori* is successfully eradicated and the patient does not require NSAID therapy, long-term acid suppression is not generally required.

## ROLE OF NSAID THERAPY

For patients in whom NSAIDs are believed causative, proscribing these medications should be done if at all possible. If NSAIDs can be discontinued, standard antacid therapy will heal the lesions. If NSAIDs must be continued, antacid therapy with a proton pump inhibitor given for 12 weeks is indicated to heal the ulcer. Prospective studies have shown the superiority of omeprazole in standard doses compared to H2 receptor antagonists and misoprostol for the healing of NSAID-related ulcers despite continued NSAID use.

Patients who require long-term conventional NSAID therapy will require cotherapy. In a study randomizing over 700 patients with healed NSAID-related gastric or duodenal ulcers, but who required continued NSAIDs, to omeprazole (20 mg/day), misoprostol (200 μg BID), or placebo, the ulcer remission rates were 61, 48, and 27% at 24 weeks, respectively. Although this study clearly documented the superiority of omeprazole, it should be recognized that almost 40% of patients had ulcer relapse, which is unacceptable.

Another strategy that could be employed is the use of cyclooxygenase-2 inhibitors (COX-2). A study comparing the COX-2 agent celecoxib to diclofenac plus omeprazole in patients with NSAID-related ulcer bleeding found an equivalent rate of recurrent bleeding at 6 months of 4.9 vs 6.4%, respectively. These results suggest that in high risk patients, a COX-2 agent alone may need to be given with a proton pump inhibitor to further reduce bleeding risk. Ongoing studies should address this important question.

The use of even low-dose aspirin increases the risk of peptic ulcer bleeding. The relative risk of even low-dose aspirin (81 mg) has been shown to be greater than 2. The risk is higher with increasing aspirin dose, given the dose–response relationship. Therefore, in the patient with a bleeding ulcer who requires long-term low-dose aspirin, cotherapy with a proton pump inhibitor should be provided.

There are some data suggesting that *H. pylori* eradication may reduce the ulcer recurrence rate despite continued NSAID use. Chan and colleagues compared maintenance omeprazole to *H. pylori* eradication in patients with bleeding ulcers who required continued aspirin or naproxyn therapy. In patients requiring naproxyn, they found the incidence of recurrent ulcer was lower in patients receiving omeprazole (4%) than in those undergoing *H. pylori* eradication alone (19%). In contrast, the recurrent hemorrhage rate was equivalent for patients receiving aspirin and omeprazole and for patients receiving aspirin and *H. pylori* eradication without omeprazole.

## SUMMARY

UGIB remains a common and important medical condition. Great strides have been made in the past decade in the development of endoscopic hemostatic techniques that have significantly impacted our ability to control and prevent rebleeding. The use of potent antiacid therapy, including intravenous proton pump inhibitors, may additionally improve the outcome of bleeding peptic ulcer. Prompt recognition of the patient with UGIB will ensure timely endoscopic evaluation, providing not only a diagnosis, but also the opportunity for endoscopic therapy and triage. Patients with low-risk lesions at endoscopy can be managed with earlier hospital discharge assuming there is no significant comorbidity.

### See Also the Following Articles

Duodenal Ulcer Endoscopy, Complications of • Gastric Ulcer • *Helicobacter pylori* • Hemorrhage • Lower Gastrointestinal Bleeding and Severe Hematochezia • Mallory–Weiss Tear • NSAID-Induced Injury • Occult Gastrointestinal Bleeding • Portal Hypertension and Esophageal Varices • Upper Gastrointestinal Endoscopy • Variceal Bleeding

## Further Reading


Bornman, P. C., Theodorou, N. A., Shuttleworth, R. D., Essel, H. P., and Marks, I. N. (1985). Importance of hypovolaemic shock and endoscopic signs in predicting recurrent haemorrhage from peptic ulceration: A prospective evaluation. *BMJ* **291**, 245–257

Chan, F. K., Hung, L. C., Suen, B. Y., Wu, J. C., Lee, K. C., Leung, V. K., Hui, A. J., To, K. F., Leung, W. K., Wong, V. W., Chung, S. C., Sung, J. J. (2002). Celecoxib versus diclofenac and omeprazole in reducing the risk of recurrent ulcer bleeding in patients with arthritis. *N. Engl. J. Med.* **26**, 2104–2110.

Chung, I. K., Kim, E. J., Lee, M. S., Park, S. H., Lee, M. H., Kim, S. J., Cho, M. S., and Hwang, K. Y. (2001). Endoscopic hemastasis on bleeding peptic ulcers. *Endoscopy* 33, 969- 975.

Chung, S. C. S., Lau, J. Y. W., and Sung, J. J. Y. (1997). Randomized comparison between adrenaline injection along and adrenaline injection plus heat probe treatment for actively bleeding ulcers. *BMJ* **314**, 1307–1311.

Cook, D. J., Guyatt, G. H., Salena, B. J., and Laine, L. A. (1992). Endoscopic therapy for acute nonvariceal upper gastrointestinal hemorrhage: A meta-analysis. *Gastroenterology* **102**, 139–148.

Derry, S., and Loke, Y. K. (2000). Risk of gastrointestinal hemorrhage with long term use of aspirin: Meta-analysis. *BMJ* 321, 1183–1187.

Grino, P., Pascual, S., Such, J., Casellas, J. A., Niveiro, M., Andreau, M., Saez, J., Grino, E., Palazon, J. M., Carnicer, F., and Perez-Mateo, M. (2001). Comparison of diagnostic methods of *Helicobacter pylori* infection in patients with upper gastrointestinal bleeding. *Scand. J. Gastroenterol.* 36, 1254–1258.

Laine, L. (1987). Multipolar electrocoagulation in the treatment of active upper gastrointestinal tract hemorrhage. *N. Engl. J. Med.* 316, 1613–1617.

Lau, J. Y., Sung, J. J., and Lam, Y. H. (1999). Endoscopic treatment compared with surgery in patients with recurrent bleeding after initial endoscopic control of bleeding ulcers. *N. Engl. J. Med.* 340, 751–756.

Lau, J. Y. W., Sung, J. J. Y., Lee, K. K. C., Yung, M. Y., Wond, S. K. H., Wu, J. C. Y., Chan, F. K. L., Ng, E. K. W., You, J. H. S., Lee, C. W., Phil. M., Chan, A. C. W., and Chung, S. C. S. (2000). Effect of intravenous omeprazole on recurrent bleeding after endoscopic treatment of bleeding peptic ulcers. *N. Engl. J. Med.* 343, 310–316.

Podila, P. V., Ben-Menachem, T., Batra, S. K., Oruganti, N., Posa, P., and Fogel, R. (2001). Managing patients with acute, nonvariceal gastrointestinal hemorrhage: Development and effectiveness of a clinical care pathway. *Am. J. Gastroenterol.* 96, 208–219.

Rutgeerts, P., Rauws, E., and Wara, P. (1997). Randomised trial of single and repeated fibrin glue compared with injection of polidocanol in treatment of bleeding peptic ulcer. *Lancet* 350, 692–696.

Udd, M., Miettinen, P., Palmu, A., Heikkinen, M., Janatuinen, E., Pasanen, P., Tarveinen, R., Kairalouma, V., Lohman, M., Mustonen, H., and Julkunen, R. (2001). Regular-dose versus high-dose omeprazole in peptic ulcer bleeding: A prospective randomized double-blind study. *Scand. J. Gastroenterol.* 36, 1332–1338.

Wilcox, C. M., and Clark, W. C. (1999). Causes and outcome of upper and lower gastrointestinal bleeding: The Grady Hospital experience. *South Med. J.* 92, 44–50.

# Upper Gastrointestinal Endoscopy

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**achalasia** Motility disorder of the esophagus in which (1) the lower esophageal sphincter does not adequately open during swallowing and (2) the contractions in the esophagus are not coordinated.
**angularis** Sharp angulation in the lesser curvature of the normal J-shaped stomach.
**antrum** Distal or lower portion of the stomach.
**benzodiazepines** Class of medications with sedating and amnestic effects.
**biopsy** Small tissue sample taken during endoscopy.
**botulinum toxin (Botox)** Neurotoxin used to relax muscle tissue.
**bougie** Flexible device used to dilate or stretch a narrowed segment of intestine.
**cardia** Upper part of the stomach just below the esophagus.
**cautery** Procedure that delivers heat to body tissue to destroy it.
**conscious sedation** Sedation to the point of diminished consciousness but not unconsciousness.
**duodenum** Portion of the small intestine just beyond the stomach.
**dysphagia** Difficulty swallowing (food becomes stuck or held up in the chest during swallowing).
**endoscope** Tubular flexible instrument used to look into the intestine.
**epigastric** Location in the central upper abdomen.
**fibrosis** Thickening and hardening of the tissues from chronic irritation or injury.
**fluoroscopy** Real-time X-ray machine used in the setting of endoscopy to monitor the position of therapeutic devices such as balloon or bougies.
**fundus** Proximal portion of the stomach.
**guide-wire** Long flexible wire used during endoscopy to guide instruments into correct position.
**hemostasis** Control of bleeding.
**hypotension** Abnormally low blood pressure.
**lower esophageal sphincter** Muscular valve at the lower end of the esophagus, at the junction with the stomach.
**Mallory–Weiss tear** Traumatic tear of the lining of the lower esophagus or upper stomach, often caused by vomiting.
**mucosa** Surface lining of the intestine.
**odynophagia** Painful sensation during swallowing.
**palliation** Relief of symptoms without curative intent.
**pylorus** Opening that leads from the stomach to the duodenum.
**retroflexing** Positioning of the tip of the endoscope so that it is turned around 180° to provide a backward view.
**savary dilator** Flexible polyvinyl dilator with a central guide-wire lumen. Used to dilate esophageal strictures
**sclerosant** Agent (usually liquid) that, when injected, causes thickening and fibrosis in tissue. Used in upper gastrointestinal endoscopy to control bleeding from a vessel.
**squamous** Normal multilayered mucosa (seen in the esophagus).
**stent** Hollow tubular device deployed in a stenosed area of bowel in order to widen the lumen diameter.
**stricture/stenosis** Narrowed portion of the intestine.
**upper esophageal sphincter** Muscular valve at the upper end of the esophagus.
**vasoconstriction** Narrowing of a blood vessel (usually a bleeding vessel).

**Upper gastrointestinal endoscopy (EGD) is the science of direct examination of the esophagus, stomach, and duodenum, using an endoscope, a flexible tube containing a light source and high-resolution optics. When connected to a monitor, an endoscope displays real-time images of the inner lining of the upper GI tract. Upper GI endoscopy may be diagnostic or therapeutic. In diagnostic endoscopy, the bowel lining is visualized but no treatment is undertaken. In therapeutic endoscopy, instruments are passed through the scope to destroy or remove tissue or deliver therapy to diseased tissue.**

## TYPES OF UPPER GASTROINTESTINAL ENDOSCOPES

Most modern upper gastrointestinal (GI) endoscopes are flexible, allowing passage through the normal turns in the human GI tract. Upper GI endoscopes are classified by external diameter and by the number and size of the working channels. Larger working channels allow passage of larger instruments used to treat bleeding and remove tissue. A detailed description of the components of endoscopes is beyond the scope of this article. Briefly, endoscopes are long flexible tubes with a light source, lens, and display monitor. The handle of the scope has buttons that enable air and water instillation and dial controls that direct the tip of the scope through the bowel. There are one or more

 

channels that run the length of the scope. These are used to aspirate fluid from the bowel, to push fluid through the scope to wash the mucosal surface, and to pass therapeutic instruments through.

## PERFORMING UPPER GASTROINTESTINAL ENDOSCOPY

### Preparation for Endoscopy

Patients must be fasting from the previous night to ensure that the upper intestine is empty. A physical examination is performed to ensure patient suitability for sedation and endoscopy. Informed consent is obtained.

### Sedation for Upper Endoscopy

In the United States, most patients are sedated for gastrointestinal endoscopy procedures. Conscious sedation is usually achieved using benzodiazepines (e.g., midazolam, diazepam) and narcotic analgesics (e.g., fentanyl, meperidine) given intravenously, the dose being titrated to the desired level of sedation. Sedation is begun immediately before the endoscopic examination and additional doses of sedative medications may be given during the procedure as needed. Patient safety is an important part of satisfactory performance of upper GI endoscopy. During and after the procedure, the patient's pulse, blood pressure, electrocardiogram (EKG), and oxygen saturation are monitored continuously. After the procedure, the sedation effect gradually wears off such that most patients may be safely discharged from the endoscopy unit within 1 h after completion of their endoscopy.

Upper GI endoscopy may be performed without sedation, as is frequently the case in Europe. However, because of the relatively large diameter of the standard diagnostic upper endoscope, unsedated upper endoscopy may be somewhat uncomfortable and will not be tolerated by all patients. Recently, an ultrathin upper endoscope was introduced in the United States. It may be used to examine the upper GI tract without sedation. This scope may be introduced into the upper GI tract either via the mouth or more commonly via the nose. In most cases, the transnasal route is preferred because during transoral passage, pressure from the scope on base of the tongue induces a gag reflex, making the procedure uncomfortable. Anxious patients are less likely to tolerate an unsedated procedure. However, in properly selected patients the upper endoscopy can be completed safely and comfortably with an ultrathin scope using this technique. In rare occurrences, it is not possible to adequately sedate a patient using standard conscious sedation agents. In that case, general anesthesia can be administered by appropriate personnel.

### Risks of Upper Gastrointestinal Endoscopy

Upper endoscopy is generally considered a safe procedure. Complications are very uncommon. The commonest serious risk of endoscopy relates not to the endoscopy procedure itself but rather to the conscious sedation administered for it. The most common unwanted side effects of sedation are respiratory depression and hypotension. Side effects are more likely to occur in the elderly and in patients with coexisting medical problems. However, with judicious dosing of sedatives and continuous careful monitoring of pulse blood pressure, EKG, and oxygen saturation during the procedure, upper endoscopy can be performed safely in most patients. Other risks of endoscopy are very uncommon and relate to injury from the scope itself, including perforation of the bowel and bleeding. Bleeding is usually minor and controllable by endoscopic techniques such as cautery and injection of vasoconstricting agents. Frank bowel perforation, though very uncommon, usually requires immediate surgical intervention.

Depending on the intent of the procedure, upper GI endoscopy can be categorized as diagnostic or therapeutic. In diagnostic endoscopy, the aim is to visualize the bowel and if necessary take small mucosal tissue samples (biopsies). In therapeutic endoscopy, active interventions, such as dilating a narrowed segment, placing a stent, or controlling bleeding, are conducted.

### Indications for Upper Gastrointestinal Endoscopy

A complete description of the medical aspects of all diseases evaluated and treated by upper GI endoscopy is beyond the scope of this article. Broadly, the indications for EGD are to diagnose and treat esophageal, gastric, and duodenal diseases. Esophageal diseases include gastroesophageal reflux disease, achalasia, and evaluation for potential injury of the esophagus from medications or toxins. Premalignant conditions of the esophagus, such as Barrett's esophagus, may be monitored endoscopically at intervals. Epigastric pain is among the commonest indications for diagnostic upper endoscopy. Disease processes in the stomach that may cause epigastric pain include gastric ulcers and gastric cancer. Persistent vomiting and vomiting of blood also require evaluation by EGD. Similarly, ulcers are among

the commonest pathologies found in the duodenum during upper endoscopy.

## The Technique of Diagnostic Upper Gastrointestinal Endoscopy

The anatomic areas visualized by upper GI endoscopy include the esophagus, the stomach, and the proximal part of the duodenum (Fig. 1). Transient views obtained during passage of the scope through the mouth and pharynx (or nose and nasopharynx in the case of transnasal endoscopy) should not be considered a substitute for a thorough evaluation by an otorhinolaryngologist.

### *Patient Position*

The patient is placed lying on his or her left side. The nurse stands near the head of the bed, monitoring the patient and suctioning excess fluid from the mouth. The endoscopist stands at the side of the bed facing the patient. A plastic bite block is placed between the patient's upper and lower teeth to protect the teeth and prevent the patient from biting the scope.

The patient is usually sedated before the scope is introduced. The scope is introduced into the upper esophagus via the oral or nasal route. The oral route is the most common. In the case of transoral upper endoscopy, the scope passes through the bite block and between the tongue and the palate. Once the scope reaches the back of the tongue, the tip is angulated approximately 90° so that it dips down into the pharynx. Using gentle pressure, the scope is advanced close to the posterior wall of the pharynx, until the upper esophageal sphincter (UES) is reached. At this time, the tip of the scope is opposed to the mucosa, limiting visualization. Gentle pressure is applied to the scope, pressing it against the UES. This pressure is sensed by the patient as an urge to swallow. Once the patient swallows, the UES opens, allowing passage of the scope into the upper esophagus. Patience is required during passage through the UES. If too much pressure is applied, perforation is risked. In some cases, the sedated patient is slow to swallow. Techniques to encourage passage of the scope through the upper esophageal sphincter include flexing the patient's neck gently forward and verbally encouraging the patient to swallow. With patience, the scope can be passed in almost every case. Occasionally, a large-diameter scope will not pass through this area. In that case, a smaller-diameter scope will usually traverse without problem. Once the scope is in the esophagus, it is gently pushed forward under direct visualization. Examination of the upper intestinal lining is performed during scope insertion or withdrawal, or both, at the discretion of the endoscopist.

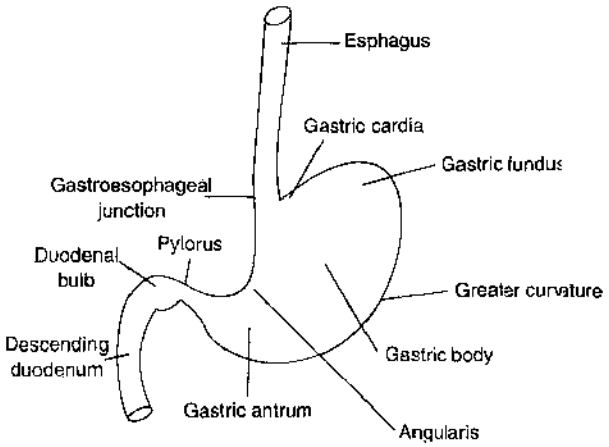


FIGURE 1 Representation of upper GI tract.

### *Examination of the Esophagus*

The mucosa (lining) of the esophagus is examined by direct visualization. The mucosa is smooth and has a gray color (Fig. 2). The scope is gently pushed slowly down the esophagus. Contractions of the esophagus may occur during examination, causing apposition of the walls and limited visualization. In that case, the endoscopist simply waits for the contraction to pass before resuming the examination. Air is instilled into the lumen of the esophagus to expand it, thus keeping it open to improve visualization. The location of

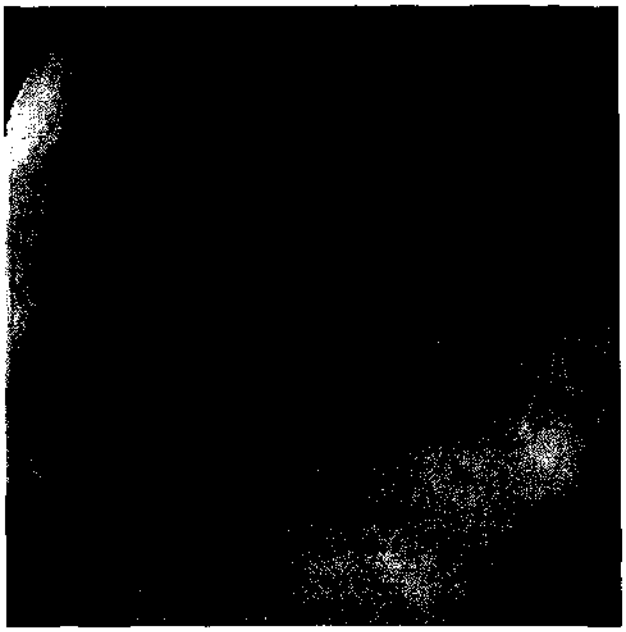

FIGURE 2 Endoscopic photograph of the normal esophagus.

anatomical landmarks within the upper intestine varies with patient size, particularly his or her height. In the average adult male, the upper esophageal sphincter is located 20 cm from the incisor teeth. The esophagus is approximately 20 cm long so the lower esophageal sphincter (LES) is located approximately 40 cm from the incisors. The muscular LES is not directly visible endoscopically, because of its location beneath the mucosa. The endoscopist will know she has reached the junction of the esophagus and the stomach when the esophageal lumen narrows and the lining changes appearance. The esophagus is lined with squamous mucosa, which has a grayish appearance. The stomach is lined by columnar mucosa, which has a salmon-colored appearance. The junction between the normal esophageal mucosa and the gastric mucosa is known as the squamocolumnar junction. In normal individuals, the squamocolumnar junction is located near the LES. There are two other important anatomical landmarks in this area. The first is the true gastroesophageal junction. This junction is determined by locating the proximal end of the normal gastric folds. In most patients, it is located in the same place as the squamocolumnar junction. Normally the esophagus passes through a hiatus in the diaphragm. At this point, the diaphragm abuts the gastroesophageal junction. In some cases, the abutment creates an impression on the bowel lumen that is visible endoscopically from inside. In patients with a hiatal hernia, this indentation is often seen in the proximal stomach.

### *Examination of the Stomach*

Once the scope passes through the gastroesophageal (GE) junction, it enters the stomach. The stomach is divided into several parts. The most proximal part located just below the GE junction is the cardia. This is best visualized by turning the tip of the scope 180°, in a maneuver known as retroflexing (Fig. 3). The body of the stomach has a wide lumen. Gastric folds extend from the cardia down through the body and become less prominent or disappear as the lower stomach (antrum) is entered. The stomach is usually J-shaped. This shape has two implications for upper endoscopy. First, the shape causes acute angulation of the stomach on the lesser curvature, at a point known as the angularis. This location must be examined carefully as this is a "blind spot" and findings here may be missed on cursory examination. Second, as the scope is advanced through the stomach, its J-shape causes the scope to become bowed against the greater curvature of the stomach, thus stretching the stomach. Excessive stretching at this point may cause the patient discomfort, sometimes to the point of inducing undesirable retching or vomiting. To avoid this problem, the scope should be advanced slowly. The gastric antrum is recognized by its smooth, flat mucosa. In the distal portion of the antrum, there is an opening that leads into the duodenum. This is the pylorus. To pass the scope beyond the stomach into the duodenum, it is advanced gently until the scope tip is opposed to the pyloric opening. Gentle pressure is maintained, while the scope tip is maneuvered to keep it in line with the pylorus. The scope tip then passes into the duodenum.

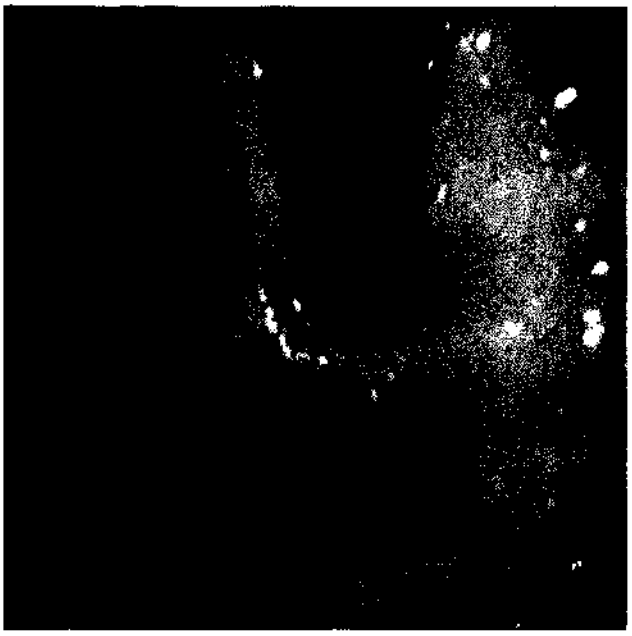

FIGURE 3 Endoscopic photograph of a retroflexed view of a normal stomach.

### *Examination of the Duodenum*

The first part of the duodenum (bulb) is recognized by its location immediately beyond the pylorus and by its flat, smooth lining. The junction between the bulb and the second portion of duodenum is angulated, requiring maneuvering of the scope to advance further. In most cases, the second portion of the duodenum is reached by advancing the scope to the end of the bulb, torquing (twisting) the scope clockwise, and deflecting the tip of the scope upward. This maneuver creates a 90° turn clockwise and the second portion of the duodenum is entered. There is a partially blind area of mucosa here. The second portion of the duodenum has prominent folds that extend most or all of the way around the lumen (Fig. 4). The scope is advanced further into the descending portion of the duodenum. The scope may be further advanced to a variable extent. This extent varies according to how much of the scope is

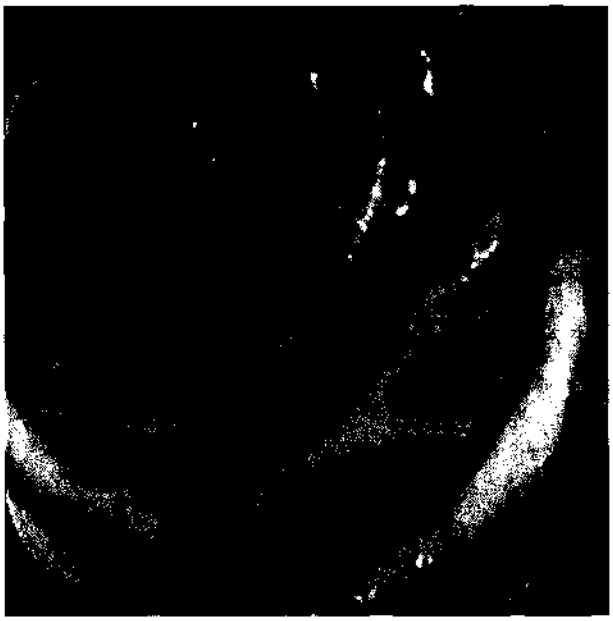

FIGURE 4 Endoscopic photograph of a normal descending duodenum.

looped or bowed in the stomach. In cases where there is much looping in the stomach, there may be insufficient scope length available to advance beyond the descending portion of the duodenum. Removing the gastric loop may help. This maneuver is known is "reducing." It is achieved by slowly pulling the scope out in small increments. As this is done, the excess scope that was previously bowed in the stomach moves away from the greater curvature and becomes available and effectively lengthens the available scope, causing the scope tip to advance despite the fact that the endoscopist is withdrawing the scope. This forward motion of the scope tip during withdrawal of the scope is known as paradoxical motion.

In most cases, detailed examination of the upper intestine is performed during withdrawal of the scope. Withdrawal from the duodenum must be done slowly, because the gastric loop will become reduced in size, causing the scope tip to rapidly pull back into the stomach. Complete visualization of the stomach requires adequate distension so that the gastric walls separate and the spaces between the gastric folds may be seen. Some portions of the stomach, especially the proximal parts, are best seen when the scope is in the retroflexed position. Air is removed by suction during withdrawal of the scope. Upon completion of the procedure, there will be some air in the intestine. The patient is encouraged to belch and to pass gas per the rectum to expel this air.

During diagnostic upper endoscopy, the endoscopist may wish to obtain a biopsy (small sample of the bowel lining) of the mucosa. In that case, a flexible wire with a small forceps at its tip is advanced through the working (biopsy) channel of the scope. When the end of the forceps is seen coming out of the scope tip, the forceps are directed to the desired part of the mucosa via a combination of advancing the forceps within the scope channel and deflecting the tip of the scope. Once the forceps are near the correct part of the mucosa, the jaws of the forceps are opened by the endoscopy assistant, by activating a lever in the handle. The open jaws of the forceps are advanced into the mucosa, pressing against it slightly so that a portion of mucosa lies between the jaws. The jaws of the forceps are then closed by the assistant, under instructions from the endoscopist. This traps a small part of the mucosa in the forceps. The tip of the forceps is quickly pulled back into the channel, thus removing a small portion of mucosa. The forceps are completely withdrawn from the biopsy channel and the tissue is retrieved from the jaws and sent for analysis.

### *Recovery after Endoscopy*

After the scope is withdrawn, the patient is sent to the recovery area and the patient's pulse, blood pressure, EKG, and oxygen saturation values are monitored for approximately 45–60 min. By that time, most of the sedation effect will have worn off and the patient will be ready for discharge from the endoscopy unit. Discharge instructions are given and follow-up arrangements are made.

## The Technique of Therapeutic Upper Endoscopy

In therapeutic upper endoscopy, the endoscopist aims to change tissue structure or anatomy by applying one or more interventions during the EGD. Choice of endoscope type is important when endoscopic therapy is planned. If an instrument channel is going to be in use for much of the therapeutic procedure, then the endoscopist will choose a scope with two working channels. One is used for the therapeutic instruments and the other is available for suctioning fluid and/or blood from the intestinal lumen or is used to flush water to wash the mucosa for better visibility. Newer endoscopes are available with very large suction channels. This allows suctioning of large pieces of solid or semisolid material from the mucosa (blood/food) to better visualize the mucosa. In therapeutic upper endoscopy, the scope is advanced into the upper GI tract

in a manner similar to that used in the diagnostic procedure.

## Common Conditions Requiring Therapeutic Upper Endoscopy

### *Esophageal Stenosis (Stricture)*

Esophageal stenoses may be benign or malignant. Different endoscopic techniques are used to dilate these two types of stenoses.

**Benign strictures** Benign esophageal stenoses are most often caused by fibrosis of the tissues in the lower esophagus as a result of chronic reflux of acid. Less common causes include postoperative, caustic (lye) injury, and pill esophagitis (medication-induced injury to the esophagus). These stenoses cause difficulty swallowing foods (mainly solid foods). Endoscopy demonstrates a narrowing of the esophagus, which in advanced cases may not allow passage of the endoscope beyond the stricture. There are two principal endoscopic techniques for dilating benign strictures: bougienage and balloon dilation.

Bougienage is dilation or stretching of the stricture using a long flexible device tapered at one end. To perform bougienage, the endoscope is removed and flexible dilators (bougies, French for candles) are guided into the esophageal stricture. This may be done blindly without a guiding system or by using a guide-wire and fluoroscopic monitoring. In the guide-wire technique, the scope is advanced to the distal stomach. A flexible metal guide-wire is placed through the working channel of the scope. The scope is withdrawn while the wire is maintained in place. At this point, the distal end of the wire is in the lower stomach and the proximal end is outside the patient's mouth. The bougie has a central channel so that it is fed over the wire and manually maneuvered into position. The position is monitored using X rays (fluoroscopy). The endoscopist will begin dilation using a small-diameter dilator, inserting and removing successively larger-diameter dilators through the stricture until the required amount of stretching is achieved. Dilation should be stopped if the patient experiences undue discomfort or if excessive resistance is felt during passage of the bougie.

Balloon dilation is performed with the scope tip in the esophagus. In balloon dilation, a long catheter is passed through the therapeutic channel of the scope. The distal end of the catheter has a deflated, sausage-shaped balloon on it. While the scope is kept in the esophagus, the balloon is slowly inflated under direct visualization in the region of the stricture, dilating it. To achieve the desired diameter of dilation, the endoscopist may use successively larger balloons. Variable-diameter balloons are available. In this case, the diameter of dilation is determined by how much air pressure is used to inflate the balloon. For benign esophageal strictures, the results from dilation using the balloons and bougies are approximately equal. The balloons have the theoretical advantage of maximizing the dilating forces and minimizing the shearing forces applied to the esophagus. However, bougies are reusable and may therefore have some cost advantages.

**Malignant esophageal strictures** Malignant strictures of the esophagus are most often caused by cancer of the lining of the esophagus itself or of the gastroesophageal junction. The patient usually presents with progressive difficulty swallowing and weight loss. When the endoscopic appearance suggests cancer, the diagnosis is confirmed with biopsies. When endoscopic palliation is deemed appropriate, the aim is to widen the esophageal lumen to allow as near normal swallowing as possible. Endoscopic treatment may include standard dilation with bougies or balloons as described above for benign strictures. However, malignant strictures restenose quickly, days or weeks after standard dilation. To prevent restenosis, a stent may be placed at the site of stricture. The most commonly used stent is the permanent self-expanding metal stent. To place this stent, the proximal and distal margins of the tumor are determined by endoscopic examination. A flexible catheter, over which a flexible stent is tightly wound, is introduced through the working channel of the scope to the narrowed area. Under direct endoscopic vision and X-ray guidance, the preloaded stent is opened. When it opens, it self-expands to widen the diameter of the esophagus at that point. Metal stents are considered permanent and once inserted are difficult or impossible to remove. In the event of recurrent narrowing, however, additional stents may be placed inside or adjacent to the original stent.

**Achalasia** To facilitate normal swallowing, the contractions in the body of the esophagus must be coordinated and the LES must open (relax) to allow the bolus of food to enter the stomach. Achalasia is a condition in which the LES valve does not relax adequately and the muscles of the main part of the esophagus do not contract in a coordinated fashion. The result is progressive problems swallowing both solid and liquid foods. Since the lack of peristalsis in the body of the esophagus cannot be reversed, the principal aim of therapy is to dilate the lower esophageal sphincter. This can be achieved endoscopically using two different techniques. The first is an injection of the neurotoxin Botox. The endoscopist performs a standard upper endoscopy. Then, using a needle on the tip of a catheter, 25 units of Botox is injected into each of the four quadrants at the

LES. This neurotoxin causes relaxation of the LES sufficient to help swallowing. The principal limitation of this treatment is that it lasts only approximately 9 months, thus requiring repeated treatments. Despite this limitation, it has a role in the management of older patients who have significant co-morbid disease and who might do poorly with riskier treatments.

The other endoscopic treatment for achalasia aims to rupture some of the muscle fibers in the LES, thus dilating it and thereby improving swallowing. This technique is called pneumatic balloon dilation. To begin, the upper GI tract is evaluated with a scope in the usual manner. A flexible wire is inserted via the scope as described in the therapeutic endoscopy section above. The scope is then withdrawn while the wire remains in place. A flexible catheter is placed over the wire under X-ray guidance. A balloon located near the distal end of the catheter is inflated and expands, stretching and rupturing the muscle fibers of the LES. The placement and inflation of the balloon are monitored under fluoroscopic guidance. The pressure in the balloon is monitored and controlled. This type of balloon dilation differs from dilation of benign peptic strictures in that the diameter of the dilating balloons is much larger (between 3 and 4 cm) and therefore the risk of perforation is higher.

**Foreign body removal** Accidentally or purposely ingested foreign bodies may be removed from the upper GI tract with the aid of endoscopy. Although small foreign bodies may pass through the GI tract without complication, larger ones that might become lodged in the small intestine are best removed endoscopically. To remove foreign bodies, upper endoscopy is performed in the usual manner. Once the foreign object is located, it is secured with a variety of different instruments, which are passed through the working channel of the scope. The instruments used to remove the foreign object include snare, forceps, net, and basket.

**Control of upper gastrointestinal bleeding** There are several causes of bleeding in the upper GI tract. The most common is acute bleeding from ulcers in the stomach or duodenum, Mallory-Weiss tears, and in patients with liver disease, varices (swollen veins) in the esophagus or proximal stomach. To control upper GI bleeding from ulcers, several endoscopic treatments may be applied. First, the site of bleeding is located and the area is washed to enhance visualization. Then a variety of liquids may be injected near the bleeding vessel to achieve hemostasis. The agents include epinephrine, which controls bleeding by its vasoconstricting effect, and alcohol, which compresses the bleeding vessel and also scleroses the surrounding tissues. Sclerosing agents such as tetradecyl are most often used to inject bleeding esophageal varices. One of the most common approaches to upper GI ulcer bleeding is to first inject the area of the vessel with epinephrine. This slows or stops the bleeding temporarily and allows better visualization. Then heat (cautery) therapy is applied. Most commonly, a cautery probe is paced through the working channel and out the tip of the scope. The tip of the probe has a bipolar coagulation device that compresses and delivers heat to the bleeding vessel. The probe is guided into position under direct visualization and is pressed firmly against the bleeding arteriole to oppose its walls. Then the probe is activated by a foot pedal, delivering heat energy to coagulate the vessel. The combination of injection with epineparine and cautery is very successful in controlling bleeding. Other hemostatic control techniques include placing a clip on the bleeding vessel or, in the case of a bleeding esophageal varix, placing a rubber band to control bleeding.

## See Also the Following Articles

Achalasia • Endoscopic Ultrasonography • Endoscopy, Complications of • Esophageal Strictures • Foreign Bodies • Gastroesophageal Reflux Disease (GERD) • Occult Gastrointestinal Bleeding • Upper Gastrointestinal Bleeding

## Further Reading

Cotton, P., and Williams, C. (1996). "Practical Gastrointestinal Endoscopy," 4th Ed. Blackwell Science Ltd., Oxford, UK.

DiMarino, A., and Benjamin, S. (2002). "Gastrointestinal Disease, an Endoscopic Approach," 2nd Ed. Slack Inc. Thorofare, NJ.

# Vagus Nerve

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**afferent fibers** Nerve components that conduct sensory information from the periphery to the central nervous system. In this context, "sensory" does not necessarily imply sensation.

**dorsal motor vagal nucleus** Brain stem nucleus where the vagal preganglionic parasympathetic neuronal cell bodies are located.

**efferent fibers** Nerve components that conduct information from the brain to the periphery. In the vagus nerve, these are predominantly preganglionic parasympathetic nerve fibers. These fibers project to the viscera and make synaptic connections with postganglionic neurones within the organs they innervate, which in turn regulate motility secretion, and blood flow. For this reason, the efferent supply is also referred to as motor innervation.

**nodose, petrosal, and jugular ganglia** Sensory ganglia; contain the cell bodies of afferent neurones that innervate the thoracic and abdominal viscera. These neurones project centrally to make synaptic connections in the nucleus of the tractus solitarius and peripherally to terminate in the viscera.

**nucleus ambiguus** Origin of motor neurones supplying the striated pharyngeal and esophageal muscles.

**nucleus of the tractus solitarius** Brain stem nucleus receiving vagal sensory input; the neurones project to the dorsal motor vagal nucleus to complete the brain stem circuit for vago-vagal reflexes and disseminate sensory information to higher brain regions.

**The vagus nerve is the Xth cranial nerve connecting the brain to the periphery, including the gastrointestinal tract. It innervates structures from the esophagus to the colon and accessory organs such as the pancreas and liver. The vagal branches supplying these various target organs contain nerve fibers that are predominantly unmyelinated, conducting action potentials at around 1 m/sec. Classically, the vagus is referred to as a parasympathetic nerve, but this relates only to its efferent functions. However, it is also an afferent nerve and conveys a vast amount of sensory information from thoracic and abdominal viscera, which serves as a basis for reflexes that control and coordinate gut function.**

## INTRODUCTION

Galen (129–199 AD), who studied dissected corpses of Roman gladiators, was probably the first anatomist to describe the distribution of the vagus nerve. With the advent of modern neurobiological techniques, the cells of origin and the terminal distributions of afferent and efferent nerve fibers of the vagus have been described in terms of topography, neurochemistry, and electrophysiology. Such studies have revealed not only the anatomy of the vagus, but also the functional basis for brain–gut interactions.

## MOTOR INNERVATION

The motor supply to the gastrointestinal (GI) tract is derived from two brain stem nuclei. The nucleus ambiguous provides the motor neurones that supply the striated muscle of the upper gastrointestinal tract, including the esophagus and the upper esophageal sphincter (Fig. 1). The preganglionic parasympathetic neurones that supply the smooth muscle portion of the gut originate in the dorsal motor vagal nucleus. This is a spindle-shaped nucleus running rostrocaudally through the medulla oblongata on either side of the central canal as it emerges into the 4th ventricle. It is organized into longitudinal columns of neurones that ultimately give rise to the different vagal branches that peal off the main anterior and posterior trunks to supply the various abdominal organs (Fig. 1). Within the gut wall, these preganglionic neurones synapse in the enteric nervous system, where the postganglionic neurones that supply the various gastrointestinal effectors are located. These effectors include the muscle layers and associated interstitial cells of Cajal, epithelia, and blood vessels, and regulate peristaltic contractions, secretions, and alterations in blood flow, respectively. In addition, vagal parasympathetic nerves can also influence resident immune cells, including macrophages and mast cells.

The textbook view of the parasympathetic innervation of the gut as being both exclusively cholinergic and entirely excitatory is outmoded. True, acetylcholine is the main neurotransmitter released from both motor and preganglionic vagal efferent fibers and, in the case of the latter, acts on nicotinic receptors located on the postsynaptic membrane of enteric neurones. However, it is now recognized that the enteric nervous system is not a simple relay station for the parasympathetic nerve

 

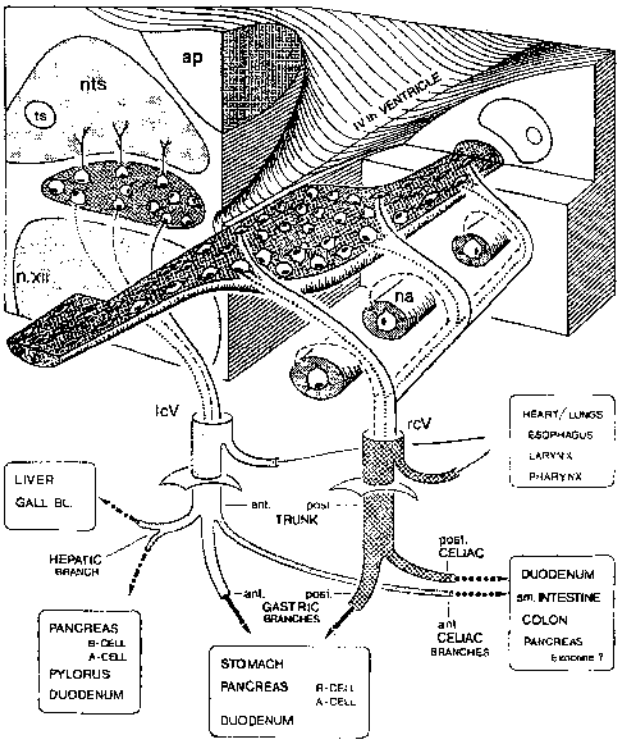


FIGURE 1 A schematic representation of the dorsal vagal complex of the medulla oblongata, viewed from a caudal and lateral (right) perspective. Also illustrated are the abdominal vagal trunks with their respective branches and a partial list of their different target tissues or organs. The dorsal motor nucleus of the vagus can be seen in a horizontal orientation on the right side of the brain stem and in a frontal orientation on the left side. The medial cell column on either side (associated, respectively, with the gastric branches) is indicated, with smaller cell bodies, and the lateral cell column on each side (associated, respectively, with the celiac branches) is indicated by larger somata. This perspective view and the different line symbols used for axons illustrate that each column of preganglionic neurons in the dorsal motor nucleus gives rise to a separate branch of the subdiaphragmatic vagus (hepatic branch neurons and axons are not shown). The nucleus ambiguous, which innervates supradiaphragmatic and striated tissues, is also illustrated on the right, where it is positioned ventrolateral and parallel to the dorsal motor nucleus of the vagus. Abbreviations: ap, area postrema; lcV, left cervical vagus; nts, nucleus of the tractus solitarius; rcV, right cervical vagus; ts, tractus solitarius; na, nucleus ambiguous. Modified by H. R. Berthoud from Ritter, S., *et al.* (1992). "Neuroanatomy and Physiology of Abdominal Vagal Afferents." CRC Press, with permission.

supply. It contains all the elements of an independent nervous system and as such can organize intrinsic reflexes to modulate contractile activity and secretion according to local demand. The enteric nervous system, in turn, is influenced by vagal preganglionic neurones and therefore provides the final pathway for both intrinsic and vagal reflexes. Acetylcholine is a transmitter in subpopulations of enteric motor neurones that innervate various effectors, and through an action on postjunctional muscarinic receptors brings about contraction or secretion. However, acetylcholine is not the only excitatory transmitter in enteric motor neurones; substance P and 5-hydroxytryptamine are examples of noncholinergic excitatory transmitters. Other enteric motor neurones contain transmitters such as adenosine triphosphate (ATP), vasoactive intestinal peptide (VIP), and nitric oxide (NO), which mediate inhibitory effects, particularly on muscle function. Consequently, vagal influence over gut function can be both excitatory and inhibitory, the latter causing relaxation of sphincters and the gastric body during accommodation of a meal or prior to emesis.

There are relatively few preganglionic vagal fibers compared to the many millions of neurones within the enteric nervous system. This fact, together with the clinical observation that gut function is relatively well maintained after vagotomy, a procedure common around the 1950s for treating peptic ulcer disease, has resulted in the importance of the vagal nerve supply being called into question. However, it is clear that the vagus nerve can have profound effects on gut function. What is intriguing, therefore, are the mechanisms that allow the enteric nervous system to maintain and restore relatively normal function in the face of a compromised vagal innervation after surgery or neuropathy.

## SENSORY INNERVATION

Afferent fibers in the abdominal vagus trunks outnumber efferent fibers by about 10 to 1. The vagus nerve can be considered more a sensory than a motor nerve, and a vast amount of sensory information is conveyed to the brain stem. The sensory cell bodies are located mainly in the nodose ganglia. These are derived from the second and third epibranchial placodes during embryonic development and project centrally to the brain stem and peripherally to their terminations in the organs they innervate. The cell bodies synthesize the transmitters and enzymes that the nerve terminals utilize in the process of synaptic transmission. Glutamate is a major excitatory transmitter for gut reflexes, but other transmitter substances exist in the brain stem, including acetylcholine, catecholamines, neuropeptides (especially tachykinins), and γ-aminobutyric acid (GABA). Within the brain stem, vagal afferents terminate mainly in the nucleus tractus solitarius (nTS), although some afferents project into the dorsal motor vagal nucleus (DMVN), where they make monosynaptic connections with vagal motorneurones. Other afferent terminals project into the area postrema (AP), a region of the brain stem that integrates peripheral and central signals

involved in triggering nausea and vomiting. From the nTS, second-order neurones project a short distance into the dorsal motor vagal nucleus to complete the vago-vagal circuits through the brain stem that help control and coordinate gut function. Other second-order neurones ascend to higher regions of the brain, including the hypothalamus and limbic system, where they modulate autonomic function and behavior.

In the periphery, vagal sensory nerve terminals branch extensively in the various layers of the gut wall. Terminals in the mucosa transmit information relevant to luminal contents, although these sensory endings do not penetrate the epithelial lining. Instead, the endings form an elaborate network within the lamina propria, where they are exposed to chemicals absorbed from the lumen (nutrients and microbial antigen) or mediators released from specific cell types in the mucosal epithelium and lamina propria. Enteroendocrine cells have a specialized apical microvillus membrane that is capable of detecting the chemical constituents of the luminal content, and in response to an appropriate stimulus, release paracrine and endocrine mediators from the basolateral aspect of the cell. One such mediator is cholecystokinin (CCK), released by fat and protein digestion products in the lumen. CCK has widespread effects on gastrointestinal function, including inhibition of gastric emptying and stimulation of pancreatic secretion and bile flow, and also contributes to the satiety mechanisms that regulate food ingestion. These effects are mediated via activation of vagal afferents that are exquisitely sensitive to CCK. Other vagal afferents are activated by 5-hydroxytryptamine (5-HT) as part of a detection system for enterotoxins. Activation of these afferents can trigger diarrhea and vomiting, which dilute and expel the potential harmful material. The receptors to these and other mediators are synthesized in the cell soma and transmitted to the periphery, where they become linked to sensory signal generation. A wide range of receptors are expressed by vagal sensory neurones, including receptors to neuromodulators, cytokines, and growth factors.

Muscle mechanosensory endings transmit information concerning the level of distension or contractile activity within the gut wall. In some regions such as the stomach, elaborate sensory terminal arrays are found in the muscle layers, where they are positioned to detect changes in muscle tone. Other endings are found in association with myenteric ganglia (intraganglionic laminar endings, or IGLEs) and can detect the activity of overlying and underlying muscles that cause distortion of their endings. The threshold for activation of these vagal mechanoreceptors, unlike spinal nociceptors that respond predominantly to high levels of distension, is within the physiological range. In other words, levels of distension or contractions associated with ongoing activity are signaled to the central nervous system (CNS).

There are also paraganglia associated with the abdominal vagus that are outside of the GI tract, and these may serve associated functions. Vagal paraganglia consist of encapsulated glomus cells and occasional neurons. Paraganglia receive blood and lymph supplies, and 90% of them are innervated by ascending afferent vagal fibers that form cuplike varicosities around glomus cells. It has been proposed that vagal paraganglia may serve as a second line of chemoreceptive defense by monitoring the blood and lymph close to the GI tract and thus modulate afferent activity.

## FUNCTIONAL ORGANIZATION OF VAGO-VAGAL REFLEXES

Sensory influences from both mucosal and mechanosensitive endings provide the CNS with a global view of the progress of digestion and the movement of contents through the gastrointestinal tract. Information on the luminal environment (pH, osmolarity, and antigen and nutrient content) and every contraction that occurs within the gastrointestinal tract is transmitted centrally to the brain. This information is used to set an appropriate parasympathetic outflow to the enteric nervous system. The enteric nervous system, in turn, integrates this parasympathetic input with local information provided by its own intrinsic sensory system. These reflexes help to match motor and secretor function to the digestive needs of the individual and coordinate gut regions that can be meters apart.

## BEHAVIORAL CONSIDERATIONS AND SENSATION

Vagal afferent information plays an important role in regulating behavior. The role of CCK in satiety and 5-HT in nausea and vomiting are well established. More controversial is the role of vagal afferents in mediating illness behavior associated with acute-phase responses following bacterial translocation across the bowel wall. Circulating cytokines, particularly interleukin-1β (IL-1β) from intestinal macrophages, play a pivotal role, but there is also evidence that vagal afferents express receptors to IL-1β and contribute to anorexia and fever associated with acute-phase responses. Mucosal mast cells respond to antigenic signals and release mediators that can also influence vagal sensory signals. Because paraganglionic glomus cells are

immunoreactive for IL-1, it is likely that vagal paraganglia also play a role in immune responses.

The role of vagal afferents in sensation is controversial. Some vagal afferents project into the cervical spinal cord and may transmit signals to spinothalamic pathways that bring about sensations such as discomfort or pain. Current evidence suggests that vagal afferent information from the nTS projects to areas of the CNS associated with emotional aspects of visceral stimulation—for example, the limbic system—rather than cognition. There is also mounting evidence that vagal afferent traffic may influence descending spinal pathways associated with pain processing. Vagal afferents may therefore modulate pain rather than mediating pain per se.

## See Also the Following Articles

**Autonomic Innervation • Cholecystokinin (CCK) • Gastric Motility • Parasympathetic Innervation • Sensory Innervation**

## Further Reading


Berthoud, H. R., and Neuhuber, W. L. (2000). Functional and chemical anatomy of the afferent vagal system. *Auton. Neurosci.* 85, 1–17.

Berthoud, H. R., Patterson, L. M., Neumann, F., and Neuhuber, W. L. (1997). Distribution and structure of vagal afferent intraganglionic laminar endings (IGLEs) in the rat gastrointestinal tract. *Anat. Embryol. (Berl.).* 195, 183–91.

Grundy, D., and Schemann, M. (2002). Motor control of the stomach. *In* "Innervation of the GI Tract" (S. Brookes and M. Costa, eds.), pp. 57–102. Taylor and Francis, New York and London.

Kirkup, A. J., Brunsden, A. M., and Grundy, D. (2001). Receptors and transmission in the brain–gut axis: Potential for novel therapies. I. Receptors on visceral afferents. *Am. J. Physiol. Gastrointest. Liver Physiol.* 280, G787-G94.

Phillips, R. J., and Powley, T. L. (2000). Tension and stretch receptors in gastrointestinal smooth muscle: Re-evaluating vagal mechanoreceptor electrophysiology. *Brain Res. Rev.* 34, 1–26.

Powley, T. L., Berthoud, H. R., Prechtl, J. C., and Fox, E. A. (1989). Fibers of the vagus nerve regulating gastrointestinal function. *In* "Brain–Gut Interactions" (Y. Tache and D. Wingate, eds.), pp. 73–82. CRC Press, Boca Raton, Florida.

Zhou, H., Ichikawa, H., and Helke, C. J. (1997). Neurochemistry of the nodose ganglion. *Prog. Neurobiol.* 52, 79–107.


# Variceal Bleeding


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**Child–Pugh classification** Assignment of the severity of cirrhosis based on clinical and laboratory parameters, including encephalopathy, ascites, bilirubin, albumin, and prothrombin time; in order of increasing severity of cirrhosis, classes A, B, and C.

**hepatic venous pressure gradient** Defined as the gradient between the wedged, or occluded, hepatic venous pressure and free hepatic venous pressure; provides a reliable measurement of portal pressure.

**primary prophylaxis** Prevention of a first variceal bleed in patients with cirrhosis and varices.

**sclerotherapy** Injection of varices with a sclerosant such as sodium morrhuate or sodium tetradecyl sulfate.

**secondary prophylaxis** Prevention of recurrent variceal hemorrhage in a patient who suffered a first episode of variceal bleeding.

**variceal band ligation** Endoscopic placement of a rubber ligature around a varix.

**Variceal bleeding, a major complication of portal hypertension resulting from cirrhosis, accounts for about 10–30% of all cases of upper gastrointestinal tract hemorrhage. More than any other cause of gastrointestinal bleeding, this complication results in considerable morbidity and mortality, prolonged hospitalization, and increased affiliated costs. Variceal hemorrhage develops in 25–35% of patients with cirrhosis and accounts for 80–90% of cases of bleeding episodes in these patients. From 10 to 30% of these episodes are fatal and as many as 70% of survivors will rebleed following an index variceal hemorrhage. Moreover, the 1-year survival is 34–80%**

and is inversely related to the severity of the underlying liver disease. Treatment of patients with gastroesophageal varices includes the prevention of the initial bleeding episede (primary prophylaxis), the control of active variceal hemorrhage, and the prevention of recurrent bleeding after a first episode (secondary prophylaxis).

## PATHOGENESIS OF GASTROESOPHAGEAL VARICES

Chronic liver disease leading to cirrhosis is the most common cause of increased portal pressure, or portal hypertension. Portal pressure is a result of the relationship depicted by Ohm's law: $P = QR$, where $P$ is the pressure along a vessel, $Q$ is the flow in the vessel, and $R$ is the resistance to that flow. In the majority of cases of liver disease, portal hypertension is the result of increased intrahepatic resistance and increased flow through the splanchnic system via a hyperdynamic circulation. Most forms of liver disease encompass aspects of each of these increases. The level of increased resistance to flow varies with specific forms of liver disease and may occur at presinusoidal or postsinusoidal levels, as in schistosomiasis and venoocclusive disease, respectively. Many forms of liver injury result in "sinusoidal" portal hypertension, the pathogenesis of which is complex but involves dynamic cellular factors (such as stellate cell constriction and contraction around sinusoids) and fixed elements (such as fibrosis). Recent studies suggest that an imbalance of the potent vasoconstrictor, endothelin-1, and the potent vasodilator, nitric oxide, may be important in the genesis of increased intrahepatic resistance, which is an early and critical component of most forms of portal hypertension.

Varices represent portosystemic collaterals derived from dilatation of preexisting embryonic vascular channels, including those between the coronary and short gastric veins and the intercostal, esophageal, and azygous veins. In the distal esophagus, over an area extending 2–5 cm from the gastroesophageal junction, veins are found more superficially in the lamina propria rather than the submucosa. This results in reduced support from surrounding tissues because of the predominant intraluminal location of these varices and may explain the predilection for bleeding at this site. The opening and dilation of portosystemic collaterals appears to depend on a threshold portal pressure gradient (portal minus free hepatic vein pressure) of 12 mm of mercury (Hg), below which varices do not form. This pressure gradient is necessary but not sufficient for the development of gastroesophageal varices. In other words, patients with gradients in excess of 12 mmHg do not invariably develop varices. The prevalence of esophageal varices in cirrhotic patients ranges from 24 to 90% and is partly related to the duration and severity of cirrhosis.

## PREDICTION OF VARICEAL HEMORRHAGE

Not all patients with varices bleed; gastroesophageal variceal hemorrhage occurs in only 30–35% of patients with cirrhosis, most commonly within 2 years of the diagnosis of varices. It is unclear what leads to rupture and bleeding in individual patients. Local factors such as changes in lower esophageal sphincter pressure or acid reflux do not appear to play a role in the pathogenesis of variceal rupture. Rather, the main determinant of bleeding is the variceal wall tension, a function of the transmural pressure, radius, and wall thickness of the vessel (as indicated by Frank's modification of LaPlace's law). Variceal rupture is directly related to physical factors such as the thickness and elastic properties of the vessel, in addition to intravariceal and intraluminal pressure. Furthermore, the severity of bleeding is related to transmural pressure and the size of the rent in the varix, and is inversely proportional to blood viscosity.

A major focus of investigation, with important clinical implications, is understanding which patients are most likely to bleed. Clinical characteristics that denote an increased risk of first variceal hemorrhage include continued alcohol use and liver decompensation, whereas endoscopic findings that predict a higher risk of bleeding include larger size of varices and the presence of endoscopic red signs (described as cherry red spots, hemocystic spots, or red wale markings) on the variceal wall, indicating dilated intraepithelial and subepithelial superficial veins. A combination of clinical and endoscopic findings, including the Child–Pugh class, size of varices, and the presence or absence of red wale markings, was found to correlate highly with the risk of first bleeding in patients with cirrhosis. Hemodynamic parameters examined include the measurement of the hepatic venous pressure gradient (HVPG), azygous blood flow, as well as direct measurement of intravariceal pressure. HVPG calculated by the gradient of wedged and free hepatic vein pressure (normal value, 5 mmHg) is used most frequently and provides reliable measurement of portal pressure in patients with cirrhosis. The extent of elevation of HVPG may be the best indicator of risk of bleeding, severity of bleeding, and survival. A rise in pressure in a patient with known varices increases the risk of bleeding, and the extent of portal pressure elevation

appears to have an inverse relationship to prognosis after hemorrhage has occurred. In general, however, a linear relationship between the degree of portal hypertension and the risk of variceal hemorrhage or variceal formation does not exist, so this technique cannot be used routinely to identify individual patients at high risk of bleeding. Of interest, the reported circadian variation in portal pressure (HVPG is highest shortly after midnight and lowest at 7 PM) may offer a possible explanation for the predilection of variceal bleeding to occur during the late evening to early hours of the day.

## PRIMARY PREVENTION OF BLEEDING FROM ESOPHAGEAL VARICES

Based on prospective studies of cirrhotic patients with varices identified at endoscopy and studies of untreated groups in randomized controlled trials, the risk of bleeding from esophageal varices has been estimated at 25–35% at 1 year. Given the poor outcome of cirrhotic patients following variceal hemorrhage, attempts have been made to identify those at high risk and prevent bleeding. In a large prospective study involving 321 patients with cirrhosis, the risk of bleeding was found to correlate with the size of varices, the presence of endoscopic red wale markings, and to the severity of liver disease. Screening endoscopy is generally recommended for patients with cirrhosis to determine the presence of large varices, but the cost-effectiveness of this approach remains controversial. The use of clinical parameters such as the presence of splenomegaly and low platelet count may help select patients likely to have large varices on endoscopy. Therapy for primary prophylaxis against variceal bleeding has evolved considerably over the past decade and is summarized in Table I.

### Pharmacologic Therapy

The general objective of pharmacologic therapy for variceal bleeding is to reduce portal pressure and consequently intravariceal pressure and wall tension. Drugs that reduce portocollateral venous flow (vasoconstrictors) or intrahepatic vascular resistance (vasodilators) have been used, and include beta-blockers, nitrates, α2-adrenergic blockers, spironolactone, pentoxifylline, and molsidomine. Because varices do not bleed at an HVPG less than 12 mmHg, reduction to this level is ideal, but substantial reductions in HVPG (i.e., by >20%) are also clinically meaningful.

Beta-blockers exert their beneficial effect on portal venous pressure by diminishing splanchnic blood flow and consequently gastroesophageal collateral and azygous blood flow. The nonselective beta-blockers, such as propranolol and nadolol, are preferred because of the dual benefit of β1- and β2-receptor blockade. β1-Receptor blockade reduces cardiac output and causes splanchnic vasoconstriction by reflex activation of α-adrenergic receptors in the splanchnic circulation, whereas β2-receptor blockade results in splanchnic and peripheral vasoconstriction by eliminating β2-receptor-mediated vasodilatation, thereby allowing unopposed α-adrenergic receptor-mediated vasoconstriction. In the absence of HVPG determination, beta-blockers are titrated in order to achieve a reduction in resting heart rate to 55 beats/minute, or 25% of baseline. Propranolol is generally given as a long-acting preparation and titrated to a maximal dose of 320 mg/day. Nadolol is initiated at 80 mg daily up to a maximal daily dose of 240 mg.

The portal pressure-reducing effects of beta-blockers are, however, unpredictable and neither the resultant reductions in heart rate nor drug blood levels are good indicators of response to therapy. For example, portal venous pressure is reduced in about 60–70% of patients who receive propranolol therapy, but only 10–30% of these patients show a substantial response (i.e., >20% reduction). Additionally, approximately 20–25% of patients have no measurable decline in portal pressure despite increasing dosage of propranolol. The effectiveness of beta-blockers for primary prophylaxis against variceal bleeding has been demonstrated in several controlled trials. Additionally, meta-analyses have revealed a 40–50% reduction in bleeding and a trend toward improved survival. Further, a cost-effectiveness analysis comparing propranolol to sclerotherapy and shunt surgery found propranolol to be the only cost-effective form of primary prophylaxis.

In addition to beta-blockers, a number of vasodilators have been investigated in portal hypertensive patients and in animal models of portal hypertension; the long-acting organic nitrates, isosorbide dinitrate and isosorbide-5-mononitrate, have received the greatest attention. Isosorbide mononitrate, the active component formed by rapid denitration of dinitrate preparations in the liver, has a relatively long half-life (about 5 hours) and dose linear kinetics even in the presence of liver or kidney disease, whereas the dinitrate preparation undergoes extensive first-pass hepatic metabolism, resulting in a short half-life and unpredictable bioavailability when used in cirrhotics. The exact mechanism of action of nitrates is unclear, but is thought to be mediated primarily by reducing intrahepatic resistance—perhaps by inhibiting sinusoidal constriction caused by hepatic stellate cells or myofibroblasts—and possibly by splanchnic arterial vasoconstriction induced in response to venous pooling and vasodilation in other

TABLE 1 Summary of Therapy for Esophageal Varices[a]

| Purpose of therapy | First-line therapy | Comments | Alternative therapy[b] | Comments |
|---|---|---|---|---|
| Primary prophylaxis[c] | Beta-blockers alone or in combination with isosorbide mononitrate[d] | Nitrate alone is not recommended; in advanced (Child–Pugh class C) liver disease, optimal therapy is unclear (probably band ligation); transplantation should be considered for patients in this group | Band ligation | Band ligation is indicated for patients with contraindications to or intolerance of medical therapy; the effectiveness of combined beta-blockers and band ligation is unknown; neither TIPS nor sclerotherapy is recommended for primary prophylaxis |
| Active variceal bleeding | Octreotide (or terlipressin) and endoscopic therapy[e] | Octreotide (or terlipressin) should be continued for a minimum of 24–28 hours; band ligation may be superior to sclerotherapy | Balloon tamponade<br>TIPS | Tamponade is indicated primarily as a temporizing measure<br>TIPS is reserved for those with refractory or recurrent early bleeding |
| | | Antibiotic prophylaxis should be considered, especially in patients with ascites | Shunt surgery | Surgery is reserved for those in whom TIPS is not feasible |
| Secondary prophylaxis[f] | Band ligation alone or in combination with beta-blockers with or without isosorbide mononitrate | The combination of band ligation and beta-blockers with or without isosorbide mononitrate is likely to be more effective than either therapy alone | TIPS | TIPS is best used as a bridge to transplantation in patients with advanced liver disease |
| | | Patients with advanced liver disease often have an intolerance to beta-blockers | Shunt surgery | Shunt surgery should be reserved for selected patients with Child–Pugh class A and class B cirrhosis |

[a] Data from Sharara and Rockey (2001).

[b] TIPS, Transjugular intrahepatic portosystemic shunt.

[c] Variceal hemorrhage occurs in 25–30% of patients within 2 years after the documentation of varices.

[d] Beta-blockers reduce the risk of variceal hemorrhage to 15–18%, and the combination of beta-blockers and isosorbide mononitrate reduces the risk to 8.5–10%. The beta-blocker propranolol is generally given as a long-acting preparation, and the dose is titrated to a maximum of 320 mg/day. The initial dose of the beta-blocker nadolol is 20 mg/day and the dose is increased up to a maximum of 80 mg/day.

[e] Octreotide is usually given as an infusion of 25–50 μg/hour (with or without a bolus). The dosage of terlipressin is 2 mg every 4 hours for the first 24 hours, then 1 mg every 4 hours.

[f] Bleeding recurs in approximately two-thirds of patients within 1 year after the initial hemorrhage.

regional vascular beds. Monotherapy with nitrates is ineffective in primary prophylaxis and may have detrimental effects, particularly in cirrhotic patients with ascites, such as accentuation of hemodynamic and laboratory signs of hypovolemia and vasodilatation, akin to those seen in what has been called postparacentesis circulatory dysfunction.

The addition of isosorbide mononitrate to propranolol has been shown to result in an enhanced reduction in portal pressure in humans. In a randomized controlled study involving 42 patients with cirrhosis and esophageal varices, a reduction of greater than 20% in HVPG was documented in only 10% in the propranolol group, compared to 50% in the combination therapy group. In patients with Child–Pugh class A and B cirrhosis, the addition of isosorbide mononitrate to nadolol has been shown, in a randomized trial, to result in a greater than 50% additional reduction in variceal bleeding rate when compared with nadolol monotherapy (12%, compared with 29%).

### Endoscopic Therapy

Over the past two decades, endoscopic therapies have assumed a prominent role in treatment of esophageal varices. Endoscopic sclerotherapy is performed by injecting a small volume of any of a number of sclerosant solutions (such as sodium tetradecyl sulfate, sodium morrhuate, ethanolamine, or absolute ethanol), usually in an intravariceal location. These sclerosing agents are all highly effective in achieving hemostasis in approximately 80–90% of patients, although their mechanisms of action are not entirely clear (e.g., local tamponade effect, or primary venous thrombosis). Multiple randomized trials have examined the effect of endoscopic sclerotherapy in the prevention of first variceal bleeding. Results are conflicting, with few trials showing significant reduction in bleeding and most showing no difference. One study was stopped prematurely because of higher mortality in the sclerotherapy group as compared to the sham-treatment group.

Band ligation of esophageal varices utilizes the same methodology employed for years in elastic band ligation of internal hemorrhoids. A suction adapter is fitted on the tip of the endoscope, the varix is suctioned into the cylinder, and a rubber band is deployed around the varix, resulting in ischemic necrosis of the mucosa and submucosa but leaving an intact muscularis propria. The resultant shallow ulcerations are replaced by granulation tissue and dense mature scar tissue and lead to variceal obliteration. The only published trial, to date, comparing ligation to propranolol in the primary prevention of variceal bleeding showed an actuarial rate of bleeding of 15% in the ligation group compared to 43% in the propranolol monotherapy group. The study was criticized, however, because of the higher than expected rate of bleeding in the propranolol group as well as the relatively low mean dose of propranolol used. Furthermore, the preliminary results of another trial published in abstract form show no advantage of ligation when compared to the combination of nitrates and beta-blockers. Nevertheless, ligation may be an acceptable option for patients at high risk of variceal bleeding and who are intolerant of, or have contraindications to, medical therapy. The optimal primary prophylaxis in patients with Child–Pugh class C cirrhosis remains unclear, and may arguably be liver transplantation.

## MANAGEMENT OF ACUTE VARICEAL HEMORRHAGE

Variceal hemorrhage is usually an acute clinical event characterized by rapid gastrointestinal blood loss presenting as hematemesis (which can be massive), with or without melena or hematochezia. Hemodynamic instability (i.e., tachycardia and/or hypotension) is common. A successful outcome in all cases of upper gastrointestinal hemorrhage, including those of variceal bleeding, hinges on prompt resuscitation, hemodynamic support, and attempt at correction of any hemostatic derangement, preferably in the setting of an intensive care unit.

Although variceal bleeding is common in patients with cirrhosis presenting with acute upper gastrointestinal hemorrhage, other causes of bleeding, such as ulcer disease, must be considered in the differential diagnosis. Urgent initiation of empiric pharmacologic therapy with vasoactive agents is indicated in situations in which variceal hemorrhage is likely. Subsequently, direct examination of the upper gastrointestinal tract by an experienced endoscopist is critical to establish an accurate diagnosis and to provide the rationale for immediate and subsequent therapies. The immediate steps in the management of acute variceal bleeding include (1) volume resuscitation, (2) prevention of complications, (3) ensuring hemostasis, and (4) initiating measures to prevent early and delayed rebleeding. Optimal volume resuscitation is the most critical aspect of management of all patients with gastrointestinal hemorrhage. Patients with suspected variceal bleeding should have large-bore intravenous lines placed and should receive crystalloids and/or blood in proportion to the degree of hemodynamic instability. Coagulopathy should also be corrected. Caution should be exercised, however, in avoiding overtransfusion because of the

theoretical concern of rebleeding from the variceal rent after excessive blood volume expansion. Although largely unsupported, it is traditional in medical training and practice to use a hematocrit of 30% as an upper safety margin following transfusion.

There is no evidence that placement of a nasogastric tube contributes to variceal rupture or bleeding. Furthermore, a nasogastric tube can be helpful in providing a crude index of the activity and amount of bleeding as well as in decompressing the stomach of blood and clots, thereby reducing the risk of aspiration. Because of the risk of aspiration, elective endotracheal intubation should be considered prior to endoscopy in patients with massive bleeding, severe agitation, or altered mental status. Patients with variceal hemorrhage and ascites are at increased risk of bacterial infections, particularly spontaneous bacterial peritonitis. This risk appears to be increased in the setting of uncontrolled hemorrhage or as a result of transient bacteremia following endoscopic sclerotherapy or variceal ligation. Short-term systemic antibiotics (e.g., third-generation cephalosporins for 4 to 10 days) have been shown, in a meta-analysis, to decrease the risk of bacterial infections and to reduce mortality in cirrhotic patients with gastrointestinal bleeding. Last, patients with cirrhosis and massive gastrointestinal hemorrhage are at risk for the development (or exacerbation of preexisting) portosystemic encephalopathy. This complication should be recognized and managed accordingly. Furthermore, it has been suggested that the presence of blood in the gut may, as a result of its large protein load, lead to reflex splanchnic hyperemia, presumably via the release of vasoactive gastrointestinal peptides. Theoretically, the resultant increase in portal venous pressure may increase the risk of early rebleeding. In support of this theory is a controlled trial from France showing a reduction in blood requirements and in mortality following whole gut irrigation with isotonic mannitol in cirrhotic patients with gastrointestinal bleeding.

## PHARMACOLOGIC THERAPY

Pharmacologic therapy can be administered early, requires no special technical expertise, and is thus a desirable first-line option for the management of acute variceal hemorrhage. Drugs that reduce portocollateral venous flow (vasoconstrictors) or intrahepatic vascular resistance (vasodilators) or both have been used in order to achieve this effect. Vasoconstrictors work by decreasing splanchnic arterial flow whereas vasodilators are used in combination with vasoconstrictors in order to reduce their systemic side effects but may also exert an added beneficial effect on intrahepatic resistance (Table 1).

### Vasopressin and Glypressin

Vasopressin is a nonselective vasoconstricting agent that causes a reduction of splanchnic blood flow and thereby a reduced portal pressure. Introduced in 1956, vasopressin was the first agent shown to reduce hemorrhage from varices. Because of its short half-life, vasopressin must be given by continuous intravenous infusion and dosage is limited because of significant systemic vasoconstriction, necessitating discontinuation of therapy in 25% of cases. Severe vascular complications such as myocardial ischemia and infarction, mesenteric and limb ischemia, and cerebrovascular accidents have been described. In addition, vasopressin prevents free water excretion from the kidneys and can result in fluid overload, hyponatremia, and worsening ascites. The concomitant use of nitroglycerin results in improved efficacy in the control of variceal hemorrhage (up to 70%) and reduction in the systemic side effects of vasopressin. The beneficial effect of nitroglycerin appears to be a result of the effect of nitric oxide on intrahepatic vascular resistance, causing a reduction in portal pressure. This favorable effect of nitroglycerin is independent of the mode of delivery (sublingual, intravenous, or transdermal). Blood pressure and electrocardiographic monitoring are recommended during therapy with vasopressin and nitroglycerin.

Triglycyllysine vasopressin (glypressin, terlipressin) is a synthetic vasopressin analogue activated *in vivo* by cleavage of its N-terminal residue. Compared with vasopressin, glypressin has fewer side effects and a longer biologic half-life, allowing its use as a bolus intravenous injection (2 mg every 4 hours for the initial 24 hours, then 1 mg every 4 hours for the next 24 to 48 hours). This advantage has led to its successful use in the "field" for cases of suspected variceal bleeding prior to or during transport to the hospital. Glypressin has been shown in multiple placebo-controlled trials to control bleeding in about 80% of cases and is the only pharmacologic therapy proven, to date, to reduce mortality from acute variceal hemorrhage. Glypressin is not currently available in the United States.

### Somatostatin, Octreotide, and Vapreotide

Somatostatin, a naturally occurring peptide, and its analogues, octreotide and vapreotide, stop variceal hemorrhage in up to 80% of patients and are generally considered to be equivalent to vasopressin, terlipressin, and endoscopic therapy for the control of acute variceal bleeding. Their precise mechanism of action is unclear but may be due to an effect on the release of vasoactive

peptides (such as glucagon, vasoactive intestinal peptide, and substance P) or to reduction of postprandial hyperemia. Somatostatin is used as a continuous intravenous infusion of 250 μg/hour following a bolus injection of 250 μg. Octreotide is used as a continuous infusion of 50 μg/hour and does not require a bolus injection. Side effects are minor, including hyperglycemia and mild abdominal cramps.

A recent area of interest has been the use of octreotide or vapreotide in combination with endoscopic therapy. In two separate studies, the addition of octreotide to endoscopic sclerotherapy or banding resulted in improved control of bleeding and reduced transfusion requirements, but did not reduce overall mortality. Based on this work, a continuous infusion of octreotide of 25 μg/hour has been recommended for 5 days following emergency endoscopic therapy. The added benefit of octreotide appears, however, to be largely limited to the first 24–48 hours of use. In one study, all early rebleeding episodes occurred within 2 days of endoscopic therapy; in the other study, no statistically significant difference was noted after the first 24 hours between the octreotide or placebo groups as far as rebleeding or the mean units of blood transfused.

## ENDOSCOPIC THERAPY

Endoscopic sclerotherapy stops variceal hemorrhage in 80–90% of cases. The advantages of sclerotherapy include its ability to achieve definitive control of bleeding under direct endoscopic vision, as well as the wide availability, ease of use, and low cost of the technique. Its drawbacks include a significant risk of local complications, including ulceration, bleeding, stricture, and perforation. Rare systemic complications have been reported, including bacteremia with endocarditis, splenic or brain abscess formation, and portal vein thrombosis.

Randomized trials in patients with acute variceal bleeding have shown that endoscopic variceal band ligation is essentially equivalent to sclerotherapy in achieving initial hemostasis. Because of the limited view with the fitted suction adapter, band ligation may technically be more difficult when bleeding is massive. The newer multiband devices allow the placement of up to 10 bands in one setting, obviating the need for repeated intubation or the need for an endoscopic overtube. Complications of endoscopic variceal band ligation (EVBL) include superficial ulcerations, transient chest discomfort, and, rarely, stricture formation.

Because of the deeper submucosal location of gastric varices, injection sclerotherapy and rubber band ligation are not usually effective in controlling acute bleeding from gastric varices. The injection of *N*-butyl-2-cyanoacrylate tissue glue or the use of large, detachable endoscopic minisnares has been shown, in small, uncontrolled trials, to be effective for bleeding gastric varices.

### Balloon Tamponade

The use of the Sengstaken–Blakemore, or Minnesota, tube for hemostasis of variceal bleeding is based on the principle of the application of direct pressure on the bleeding varix by an inflatable (esophageal or gastric) balloon fitted on a rubber nasogastric tube. It is important to note that only physicians experienced in this technique should place these tubes. When properly applied, balloon tamponade is successful in achieving immediate hemostasis in almost all cases. However, early rebleeding following balloon decompression is high. Complications of balloon tamponade include esophageal perforation or rupture, aspiration, and asphyxiation from upper airway obstruction. Balloon tamponade is generally not recommended and should largely be reserved for rescue of cases of hemorrhage uncontrolled by pharmacologic and endoscopic methods and as a temporary bridge to more definitive therapy.

### Transjugular Intrahepatic Portosystemic Shunt

Treatment with a transjugular intrahepatic portosystemic shunt (TIPS) consists of the vascular placement of an expandable metal stent across a tract created between a hepatic vein and a major intrahepatic branch of the portal system. TIPS can be successfully performed in 90–100% of patients, resulting in hemodynamic changes similar to a partially decompressive side-to-side portacaval shunt but avoiding the morbidity and mortality associated with a major surgical procedure. TIPS as been shown to be effective in the treatment of refractory, uncontrolled, acute variceal bleeding. Of note, patients with advanced liver disease and multiorgan failure at the time of TIPS have a 30-day mortality that approaches 100%.

### Surgical Therapy

Surgery is generally considered in the setting of continued hemorrhage or recurrent early rebleeding (uncontrolled by repeated endoscopic or continued pharmacologic therapy) and when TIPS is not available or technically feasible. Surgical options include portosystemic shunting or esophageal staple transection alone or with esophagogastric devascularization and

splenectomy (Sugiura procedure). Devascularization procedures may be useful in patients who cannot be shunted because of splanchnic venous thrombosis. Regardless of the choice of surgical technique, morbidity is high and the 30-day mortality for emergency surgery has approached 80% in some series. Understandably, "rescue" liver transplantation is not a practical option for patients with uncontrolled variceal hemorrhage.

## PREVENTION OF RECURRENT VARICEAL BLEEDING

Variceal hemorrhage recurs in approximately two-thirds of patients, most commonly within the first 6 weeks after the initial episode. This period of high risk can be subdivided into an early (first 5 days) and a late period, with the highest risk falling within the first 5 days from the initial hemorrhage. As mentioned previously, the risk of early rebleeding is reduced by the adjuvant use of octreotide or vapreotide and possibly glypressin and somatostatin, primarily in the first 24 to 48 hours, after initial endoscopic or pharmacologic control of hemorrhage. Risks for early rebleeding include clinical, endoscopic, and hemodynamic parameters, such as the severity of the initial bleed, the degree of liver decompensation, and the presence of encephalopathy and impaired renal function. Endoscopic parameters predictive of early rebleeding include the presence of active bleeding, stigmata of recent bleeding, and/or large varices. The severity of portal hypertension correlates closely with the severity and risk of rebleeding as well as actuarial probability of survival following an index episode. In a cohort of patients presenting with variceal hemorrhage, those with an initial HVPG greater than 20 mmHg had a 1-year mortality of 64% compared to 20% for patients with lesser elevations in portal pressure.

Given the high risk of recurrent hemorrhage and its associated morbidity and mortality, strategies aimed at prevention should be rapidly instituted following the index episode (Fig. 1). The choice of preventive therapy should, therefore, take into consideration the efficacy of therapy, the side effects of the selected treatment, the patient's expected survival, and overall cost. Preventative strategies include pharmacologic, endoscopic, and surgical methods.

### Pharmacologic Therapy

Reducing the portal pressure by more than 20% from the baseline value pharmacologically results in a reduction in the cumulative probability of recurrent bleeding at 1, 2, and 3 years from 28% at 1 year, 39% at 2 years, and 66% at 3 years, to 4, 9, and 9%,

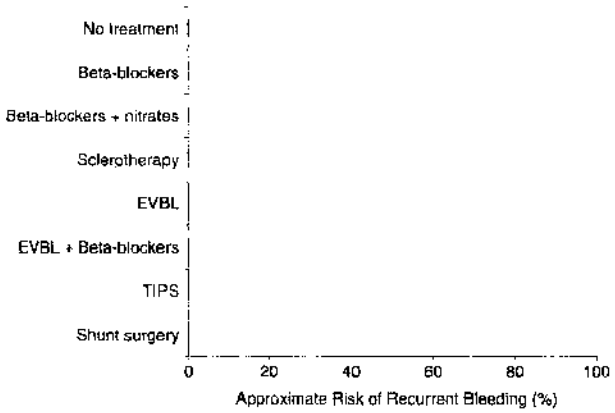


**FIGURE 1** Relative effectiveness of available therapies for the prevention of recurrent variceal bleeding. The estimates shown are based on the cumulative data available in the literature (recurrent bleeding at 1 year). EVBL, Endoscopic variceal band ligation; TIPS, transjugular intrahepatic portosystemic shunt. Reproduced with permission from Sharara and Rockey (2001).

respectively. Although adjustment of medical therapy based on portal pressure measurement would be ideal, HVPG determination may not be readily available, thus therapy must be adjusted using empiric clinical parameters.

Agents with a favorable effect on portal pressure in humans with cirrhosis include beta-blockers, nitrates, α2-adrenergic blockers, spironolactone, pentoxifylline, and the venous dilator molsidomine. However, the most widely used drugs and the only ones for which there is sufficient evidence are the nonselective beta-blockers (which have been used with or without oral nitrates). Several randomized placebo-controlled trials, including a meta-analysis, have demonstrated that beta-blockers prevent rebleeding and prolong survival. The major side effects of beta-blockers are fatigue, impotence, depression, bradycardia, hypotension, and sleep disorders. Contraindications to therapy include congestive heart failure, asthma or chronic obstructive pulmonary disease, and atrioventricular heart block.

The addition of isosorbide mononitrate to beta-blockers appears to enhance the protective effect of beta-blockers alone for the prevention of recurrent variceal bleeding, but offers no survival advantage and reduces the tolerability of therapy. Compared with either sclerotherapy or endoscopic band ligation, combination medical therapy is superior in reducing the risk of recurrent bleeding in patients with esophageal variceal hemorrhage, primarily in patients with Child–Pugh class A and B cirrhosis. Notably, in patients who show a significant hemodynamic response to therapy (defined as a reduction in the hepatic venous pressure

gradient to less than 12 mmHg or more than 20% of the baseline value), the risk of recurrent bleeding and of death is significantly reduced.

## Endoscopic Therapy

Endoscopic therapy has been established over the past decade as a therapeutic cornerstone for prevention of esophageal variceal rebleeding. Gastric varices, however, are not effectively treated by sclerotherapy or ligation. Patients with recurrent gastric variceal hemorrhage are best treated by *N*-butyl-2-cyanoacrylate injection or by nonendoscopic means.

Sclerotherapy reduces the risk of recurrent esophageal variceal bleeding from approximately 65% to 30–35% at 1 year, but does not appear to improve overall mortality. Sclerotherapy is performed every 10–14 days until varices are eradicated, usually after five or six sessions. A meta-analysis of nine trials found endoscopy and beta-blockers to be equivalent with respect to the risk of rebleeding and survival. Moreover, combination pharmacotherapy (beta-blockers plus isosorbide-5-mononitrate) is superior to sclerotherapy alone in patients with Child–Pugh class A or B cirrhosis.

Endoscopic variceal band ligation is highly effective at obliterating varices. Ligation is associated with a lower risk of recurrent bleeding, compared to sclerotherapy (approximately 25 vs. 30% at 1 year), fewer complications, reduced overall cost, and higher survival. Ligation should, therefore, be considered standard endoscopic therapy for secondary prophylaxis. As with sclerotherapy, ligation is performed every 10 to 14 days until complete variceal eradication, typically requiring three or four sessions.

Combination modality approaches, usually including an endoscopic and pharmacologic treatment, are attractive pathophysiologically and may be more effective than single therapy. Combined endoscopic therapy and beta-blockers reduce recurrent bleeding more than do beta-blockers alone (but provide no survival benefit). Although addition of sclerotherapy to ligation may theoretically offer greater protection against recurrent bleeding, this combination has not been shown to be advantageous.

## Transjugular Intrahepatic Portosystemic Shunt

Transjugular shunting is more effective than endoscopic therapy for preventing variceal rebleeding but offers no survival benefit. The cumulative risk of rebleeding following TIPS placement is 8–18% at 1 year. The trade-off, however, is that TIPS is associated with a higher incidence of clinically significant hepatic encephalopathy (new or worsened portosystemic encephalopathy is noted in about 25% of patients after TIPS). Advanced liver disease is the main determinant of poor outcome following TIPS. Consequently, in patients with advanced liver disease, TIPS is best used as a bridge to liver transplantation.

An important concern with TIPS is the development of shunt stenosis and/or occlusion due primarily to pseudointimal hyperplasia, with reported rates of 31% at 1 year and 47% at 2 years. Doppler ultrasound examination of the stent is routinely performed at some centers to examine blood flow and estimate the shunt patency, but has a low sensitivity and specificity. Balloon dilatation of the stenosed stent or redeployment of another metallic prosthesis is done in case of significant stenosis. Management of hepatic encephalopathy and shunt stenosis may result in significant affiliated costs when TIPS is considered. A cost analysis comparing TIPS and endoscopic sclerotherapy has suggested no difference in cumulative cost despite the lower incidence of rebleeding with TIPS.

## Surgical Therapy

Portosystemic shunt surgery is the most effective means by which to reduce portal pressure. Although effective at eradicating varices and preventing rebleeding, nonselective portacaval shunts are associated with a significant incidence of hepatic encephalopathy, portal vein thrombosis, and occasionally liver failure. In contrast, selective shunts decompress the portal system without endangering portal blood flow, liver function, or the feasibility of future liver transplantation. It is important to note that elective surgical therapy is largely reserved for patients with Child–Pugh class A disease and a proportion of patients with class B disease and preserved liver function. The choice of surgical therapy should be individualized and must be considered in the context of cause and severity of liver disease, patient compliance, likelihood of liver disease progression, and overall prognosis. Surgery may be preferred in patients who are not likely to be compliant with medical or repeated endoscopic therapy, or those that are not candidates for liver transplantation (e.g., active substance abuse, HIV positive).

Commonly used shunts include the distal splenorenal shunt and the low-diameter (mesocaval or portacaval) interposition shunt. Rates of recurrent bleeding are on the order of 10%, with the highest risk of bleeding occurring in the first month after surgery. Devascularization procedures (i.e., esophageal

transection and gastroesophageal devascularization) are usually considered in patients who cannot undergo shunts because of splanchnic venous thrombosis and should be performed only by experienced surgeons.

## COST-COMPARISON OF AVAILABLE THERAPIES

Data examining the cost of variceal bleeding and the cost-effectiveness of commonly used therapies are limited. The treatment cost of an episode of variceal bleeding has been estimated at $10,000 to $35,000. Further, the cost-effectiveness of diagnostic methods used to guide therapy is unclear. For example, HVPG determination, which may accurately predict pharmacologic response to therapy, is an attractive, although invasive, adjunct in the management of patients with variceal bleeding, but its cost-effectiveness is an open question. Further, screening endoscopy for detection of large varices, although recommended, has not been demonstrated to be cost-effective.

Finally, there are areas in which management is controversial and not standardized. For example, given the right expertise, secondary prophylaxis with surgical shunts may be more effective than medical or endoscopic therapy in Child–Pugh class A patients. On the other hand, patients with advanced cirrhosis are often intolerant of beta-blockers—let alone in combination with nitrates—and therefore the use of combination therapy remains controversial in such patients. Arguably, the preferred treatment for such patients is early liver transplantation. Therefore, when choosing a specific treatment plan, the clinician must take into consideration the direct costs of health care utilization, as well as the efficacy and morbidity of therapy. The treatment chosen should be tailored to fit the patient's clinical condition while also taking into account the possibility that the patient's liver disease may progress and thus necessitate transplantation. Furthermore, the cost-effectiveness of various treatment modalities should factor in the cost of failed therapy (e.g., rebleeding, shunt revision) and that of treatment-related complications (encephalopathy, esophageal stricture, etc.). Therapeutic modalities used in patients with acute variceal hemorrhage, or in primary and secondary prophylaxis, are listed in Table II.

**TABLE II Efficacy and Cost of Treatment for Prevention of Recurrent Variceal Bleeding in Patients with Cirrhosis[a]**

| Treatment | Characteristics of suitable patients[b] | Risk of bleeding at 12 months[c] (%) | Cost at 12 months[d] ($) | Comments |
|---|---|---|---|---|
| Medical therapy (nadolol or propranolol and isosorbide mononitrate) | Child–Pugh class A or B cirrhosis; reduction of ≥20% in HVPG with medication; high degree of compliance | 4–25 | 3000–3700 | Includes cost of HVPG determination at baseline and at 1–2 months of therapy |
| Endoscopic variceal band ligation | Child–Pugh class A–C cirrhosis; compliance with repeated medical therapy | 20–30 | 8500–9500 | Estimate based on a mean of four sessions until varices are obliterated followed by diagnostic esophagoscopy at 3 and 12 months |
| Transjugular intrahepatic portosystemic shunt | Current or future candidates for liver transplantation | 8–15 | 12,000–15,000 | Includes cost of Doppler ultrasonography of shunt every 3 months to monitor for stenosis or occlusion |
| Distal splenorenal shunt or low-diameter (mesocaval or portocaval) interposition shunt | Child–Pugh class A or B; good liver function | 5–10 | 25,000–40,000 | Includes preoperative venous phase arteriography and measurement of liver volume |

[a] Data from Sharara and Rockey (2001).
[b] HVPG, Hepatic venous pressure gradient.
[c] The risk of bleeding varies with the severity of the liver disease.
[d] Costs represent the hospital charges, where applicable. The cost of care for bleeding episodes is not included.

## SUMMARY

Gastroesophageal variceal hemorrhage is a common and devastating complication of portal hypertension and is a leading cause of morbidity and mortality in patients with cirrhosis. Because the clinical outcomes are poor once variceal bleeding has occurred, primary prophylaxis with beta-blockers is indicated but the role of endoscopic ligation deserves further evaluation. The treatment of acute variceal hemorrhage is aimed at volume resuscitation and ensuring hemostasis with pharmacologic agents and endoscopic techniques. A high risk of rebleeding after an index episode mandates the institution of preventative strategies. Wedge pressure-guided medical therapy may be the preferred mode of secondary prophylaxis in patients with Child-Pugh class A or B cirrhosis, but treatment with a combination of methods is pathophysiologically attractive. The choice of therapy should be tailored to fit the patient's clinical condition, risk factors, and prognosis.

## See Also the Following Articles

**Cirrhosis • Esophageal Strictures • Hemorrhage • Portal Hypertension and Esophageal Varices • Somatostatin • Upper Gastrointestinal Bleeding • Upper Gastrointestinal** Endoscopy

## Further Reading

Feu, F., Garcia-Pagan, J. C., Bosch, J., *et al.* (1995). Relation between portal pressure response to pharmacotherapy and risk of recurrent variceal haemorrhage in patients with cirrhosis. *Lancet* **346**, 1056–1059.

Garcia-Pagan, J. C., Feu, F., Bosch, J., and Rodes, J. (1991). Propranolol compared with propranolol plus isosorbide-5-mononitrate for portal hypertension in cirrhosis. A randomized controlled study. *Ann. Intern. Med.* 114, 869–873.

Laine, L., and Cook, D. (1995). Endoscopic ligation compared with sclerotherapy for treatment of esophageal variceal bleeding. A meta-analysis. *Ann. Intern. Med.* 123, 280–287.

Merkel, C., Marin, R., Sacerdoti, D., *et al.* (2000). Long-term results of a clinical trial of nadolol with or without isosorbide mononitrate for primary prophylaxis of variceal bleeding in cirrhosis. *Hepatology* **31**, 324–329.

Moitinho, E., Escorsell, A., Bandi, J. C., *et al.* (1999). Prognostic value of early measurements of portal pressure in acute variceal bleeding. *Gastroenterology* **117**, 626–631.

Poynard, T., Cales, P., Pasta, L., *et al.* (1991). Beta-adrenergic-antagonist drugs in the prevention of gastrointestinal bleeding in patients with cirrhosis and esophageal varices. An analysis of data and prognostic factors in 589 patients from four randomized clinical trials. Franco-Italian Multicenter Study Group. *N. Engl. J. Med.* **324**, 1532–1538.

Polio, J., and Groszmann, R. J. (1986). Hemodynamic factors involved in the development and rupture of esophageal varices: A pathophysiologic approach to treatment. *Semin. Liver Dis.* **6**, 318–331.

Rossle, M., Deibert, P., Haag, K., *et al.* (1997). Randomised trial of transjugular-intrahepatic-portosystemic shunt versus endoscopy plus propranolol for prevention of variceal rebleeding. *Lancet* **349**, 1043–1049.

Sharara, A. I., and Rockey, D. C. (2001). Gastroesophageal variceal hemorrhage *N. Engl. J. Med.* **345**, 669–681.

Sung, J. J., Chung, S. C., Yung, M. Y., *et al.* (1995). Prospective randomised study of effect of octreotide on rebleeding from oesophageal varices after endoscopic ligation. *Lancet* **346**, 1666–1669.

The North Italian Endoscopic Club for the Study and Treatment of Esophageal Varices (1988). Prediction of the first variceal hemorrhage in patients with cirrhosis of the liver and esophageal varices: a prospective multicenter study. *N. Engl. J. Med.* **319**, 983–989.

Villanueva, C., Minana, J., Ortiz, J., *et al.* (2001). Endoscopic ligation compared with combined treatment with nadolol and isosorbide mononitrate to prevent recurrent variceal bleeding. *N. Engl. J. Med.* **345**, 647–655.

# Vascular Abnormalities

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angiodysplasia (vascular ectasia) Most common vascular abnormality of the gastrointestinal tract. Believed to be acquired with aging, represents the most frequent cause of recurrent lower intestinal bleeding in persons older than 50 years. The likely cause is intermittent, low-grade obstruction of the submucosal veins at the site where the veins penetrate the muscular layer of the colon.

angiography Radiographic technique by which blood vessels and vascular abnormalities can be visualized following injection of contrast material (dye).

Dieulafoy's lesion Rare cause of massive gastrointestinal bleeding; results from a large artery in abnormally close contact with the lining of the stomach or small intestine.

hemangioma Vascular tumor that can be found in the small intestine and colon; considered the second most common vascular lesion of the colon (after angiodysplasia). Hemangiomas can be classified into two distinct types, capillary hemangiomas and cavernous hemangiomas. They can become very large and present with gastrointestinal bleeding.

telangiectasia Vascular abnormality of small veins, arteries, and capillaries of the gastrointestinal tract. The abnormal vessels can become dilated, thin, and fragile, causing gastrointestinal bleeding. Telangiectasias are most commonly seen in the stomach and small intestine and tend to be multiple rather than single.

**Vascular abnormalities are important causes of gastrointestinal bleeding. They may be single or multiple, or part of a systemic disorder that is acquired or inherited. The most commonly occurring vascular lesions in the gastrointestinal tract are vascular ectasia, gastric antral vascular ectasia, hereditary hemorrhagic telangiectasia, progressive systemic sclerosis, Dieulafoy's lesion, hemangioma, cavernous hemangioma of the rectum, blue rubber bleb nevus syndrome, and Klippel–Trenaunay–Weber syndrome.**

## VASCULAR ECTASIA

Vascular ectasia, also referred to as angiodysplasia, is the most common vascular abnormality of the gastrointestinal (GI) tract and likely represents the most frequent cause of recurrent major lower intestinal bleeding in persons older than 50 years. Vascular ectasias are believed to be associated with the degenerative changes of aging and are not related to other vascular abnormalities of the skin or other organs. Although these lesions are occasionally seen in the upper GI tract (stomach and small intestine), they are primarily found in the right side of the colon (cecum and ascending colon). Vascular ectasias are found equally in men and women. The lesions are usually multiple and tend to be smaller than 10 mm in diameter.

Approximately 50% of patients with bleeding ectasias have some degree of cardiac disease. Up to 25% have been reported to have stenosis of the aortic valve, although recent studies have not shown such an association. There is even some anecdotal evidence that replacement of the aortic valve in severe aortic stenosis has stopped recurrent gastrointestinal bleeding from angiodysplasias. The exact relationship between ectasias, aortic valve disease, and GI bleeding is still inconclusive and needs further research. Other diseases have been associated with vascular ectasias, including a coagulation disorder (von Willebrand's disease) and chronic renal failure requiring hemodialysis, but these associations require confirmation.

### Pathology

Vascular ectasias are believed to be degenerative lesions that are acquired through aging. The likely cause is partial, intermittent, low-grade obstruction of the submucosal veins at the site where the veins penetrate the muscular layer of the colon (Fig. 1). Repeated episodes of elevated pressure during muscular contraction and distension of the right colon may ultimately result in dilatation and distortion of the submucosal vein. When resected segments of colon are injected with silicone rubber to fill the vascular lesions and then viewed under a microscope, a dilated, tortuous submucosal vein is often the earliest abnormality noted. Later, the venules and capillaries that drain into that vein may dilate and extend very close to the surface of the colon. Eventually, the sphincter regulating flow between the artery and submucosal vein becomes destroyed, allowing free flow between these vessels (arteriovenous fistula). In the most severe lesions, the innermost lining of the bowel, the mucosa, may ultimately be replaced by a maze of dilated, fragile vascular channels. Despite their complicated

 

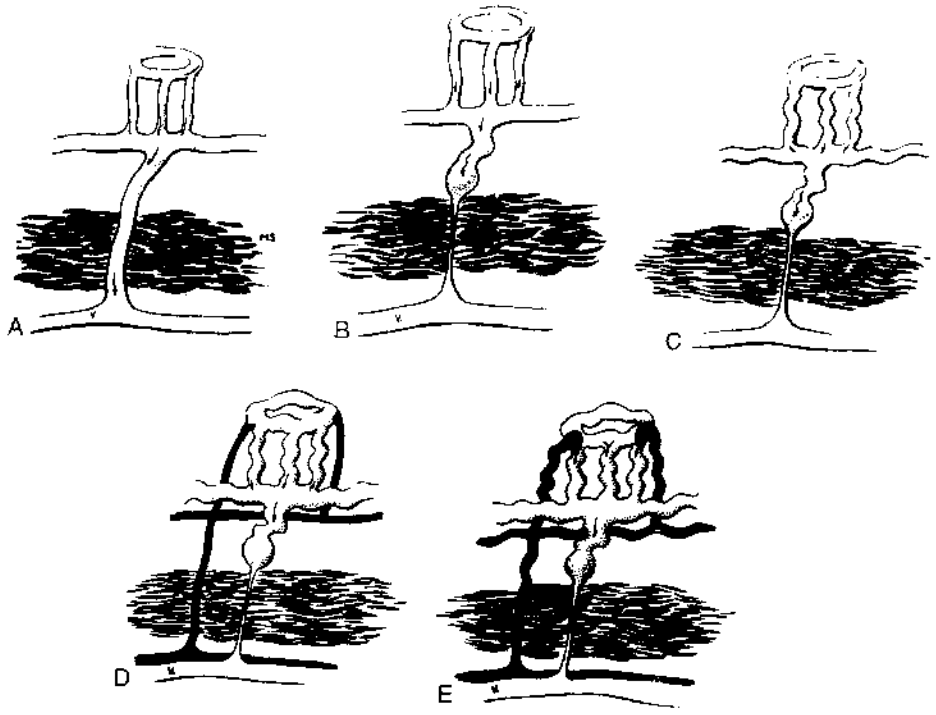


**FIGURE 1** Vascular ectasia. Proposed concept of the development of vascular ectasias: (A) Normal state of vein (v.) perforating muscle layers; (B) with muscular contraction or increased intraluminal pressure, the vein is partially obstructed; (C) after repeated episodes over many years, the submucosal vein becomes dilated and tortuous; (D) later the veins and venules draining into the abnormal submucosal vein become similarly involved; (E) ultimately the capillary ring becomes dilated, the precapillary sphincter becomes incompetent, and a small arteriovenous communication is present through the ectasia. From Boley, S. J., Sammartano, S. J., Adams, A., *et al.* (1977). On the nature and etiology of vascular ectasias of the colon: Degenerative lesions of aging. *Gastroenterology* **72**, p. 650, with permission.

appearance, vascular ectasias are often tiny—smaller than a pinhead. Local factors may play a role in the development of these lesions. For example, the greater tension in the wall of the right colon and cecum compared to the rest of the colon may be responsible for the increased prevalence of ectasias in that part of the colon.

## Clinical Presentation

Vascular ectasias manifest only through gastrointestinal bleeding. Incidental ectasias may be seen at colonoscopy in 3–6% of healthy, asymptomatic people, and require no treatment given the overall low risk of bleeding and the inability to predict who will and who will not bleed. Bleeding may be brisk or occult and the clinical presentation varies from overt passage of large amounts of bright red blood per rectum to iron-deficiency anemia. The majority of patients with colonic lesions present with chronic, low-grade bleeding. A quarter of patients may pass dark, tarry stools. A majority of the bleeding episodes stop spontaneously. Many patients have multiple blood transfusions and endoscopic procedures before a diagnosis of vascular ectasias is made.

## Diagnosis

A majority of the ectasias are diagnosed by colonoscopy, and because most are located in the right colon, it is important that the entire colon be examined. The endoscopic appearance of colonic lesions can be variable. Most often they are small in size, have scalloped or frondlike edges, and resemble a spider or a coral reef. Endoscopic diagnosis, however, is limited by the similar appearance of other vascular lesions and of even minor trauma from the colonoscopy. Circulating blood volume, the patient's state of hydration, and sedative medications (such as meperidine) also can diminish the prominence of some vascular ectasias. Blood transfusions, intravenous fluids, or administration of naloxone (which rapidly reverses the effects of meperidine) may facilitate visualization of these vascular

abnormalities. Color images of these and other lesions can be found on-line at several web sites, including the GASTROLAB Image Gallery (http://www.gastrolab.net/pawelcom.htm.). Angiography may be used to detect angiodysplasias not seen at endoscopy or to find and treat actively bleeding lesions. Knowledge of typical angiographic signs enables a more specific diagnosis than can be made by colonoscopy.

### Treatment

In most patients, bleeding can be controlled without surgery either colonoscopically or through an angiographic catheter. Endoscopic obliteration treatments include heater probe, argon plasma coagulation, and, less commonly, electrocoagulation and laser therapy. Bleeding may recur in as many as 50% of patients, prompting further therapy. A variety of medications infused though an angiographic catheter can also successfully stop bleeding, though this is rarely necessary. The most commonly used medication is vasopressin (a potent constrictor of blood vessels). As a last resort, surgical removal of the right colon is used for bleeding that does not respond to the above therapies or in circumstances in which such therapies are not available.

## GASTRIC ANTRAL VASCULAR ECTASIA: "WATERMELON STOMACH"

Gastric antral vascular ectasia (GAVE) is an unusual vascular abnormality, distinct from other vascular lesions. It has been known as "watermelon stomach" based on its appearance of dilated blood vessels radiating outward from the pylorus like spokes from a wheel, and resembling the stripes on the surface of a watermelon.

### Epidemiology

GAVE is seen commonly in older patients, the average age being 70 years. This disorder is more common in women. The cause is uncertain, but it has been associated with certain immunologic disorders, cirrhosis of the liver (especially when complicated by hypertension in the portal venous system of the liver), and absence of acid production by the stomach. No disease association has been strong enough to produce insight into the etiology of this disorder.

### Pathology

Microscopically, the mucosa of the gastric antrum is hypertrophied and folded. The vascular channels are located primarily in the submucosa and are tortuous, dilated, and contain focal thromboses. The lesion is restricted to the gastric antrum, but may be associated with other vascular disorders of the stomach if portal hypertension is present.

### Clinical Presentation and Diagnosis

Nearly all patients present with iron-deficiency anemia from slow oozing of blood, but patients may also present with overt gastrointestinal bleeding. Diagnosis is made by the characteristic endoscopy appearance of alternating red stripes with normal mucosa. Convoluted columns of ectatic vessels produce the reddish color. Angiography has not proved to be helpful in the diagnosis of these lesions.

### Treatment

Medical, endoscopic, and surgical approaches have all been utilized in the treatment of GAVE. Medical therapy is mainly that of iron replacement for anemia. Estrogen–progesterone combinations have been tried with some regression of these lesions, but results have not been consistent. GAVE lesions respond to a variety of endoscopic modalities, including heater probe, electrocoagulation, lasers, or argon plasma coagulation. Surgical resection of the gastric antrum is curative but should be considered only for patients for whom endoscopic therapy has been unsuccessful.

## HEREDITARY HEMORRHAGIC TELANGIECTASIA

A familial disorder associated with multisystem disease, hereditary hemorrhagic telangiectasia (HHT), or Osler–Weber–Rendu disease, is characterized by recurrent gastrointestinal bleeding from small vascular lesions (telangiectases) of the skin and mucous membranes. It is inherited in an autosomal dominant fashion. This disorder usually presents with recurrent nosebleeds during childhood, but the typical lesions on the lips and tongue may not be seen until later in life. Gastrointestinal bleeding is rare before age 30 years and has a peak incidence in the sixth decade. Bleeding typically improves during pregnancy. Gastrointestinal bleeding may be quite severe and some patients have received more than 50 blood transfusions over their lifetime.

### Pathology

The major abnormalities are of small veins (venules), small arteries (arterioles), and capillaries. The ends of these vessels become dilated, tortuous, and irregular. The vessels are lined by a single layer of cells without muscle or elastic tissue, so they cannot contract.

This renders them thin and very fragile and may explain why they tend to bleed.

### Clinical Presentation

Typical features of HHT include a family history in up to 80% of patients, as well as characteristic telangiectasias on the vermilion border of the lips, oral and nasal mucosae, tongue, and nailbeds. These vascular lesions may occur in the colon but are more commonly seen in the stomach and small bowel. It is at these sites where they are more likely to cause significant bleeding. Most patients will pass dark, tarry stools (melena), but vomiting of blood and the passage of red blood per rectum have also been reported. This disease is a systemic illness, and lesions are not confined to the GI tract. The telangiectasias may also be found in the lungs, brain, and liver. Pulmonary lesions may allow for shunting of pulmonary arterial blood into the cerebral circulation, which can have devastating consequences, including stroke and brain abscess.

### Treatment

The management of GI bleeding in patients with HHT is difficult because of the multiplicity of lesions. Endoscopic ablation may be performed during active bleeding or between bleeding episodes. Oral estrogen–progesterone therapy has also been used, but its effectiveness is limited. Surgical resection should be reserved for bleeding lesions resistant to endoscopic therapy, especially because rebleeding from other areas of the gastrointestinal tract is common.

## PROGRESSIVE SYSTEMIC SCLEROSIS (SCLERODERMA)

Telangiectactic vascular lesions are a prominent feature of progressive systemic sclerosis, especially in the variant that has as it clinical features calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias (CREST). In this disorder, the sites most frequently involved are the hands, lips, face, and tongue, but gastrointestinal bleeding has been reported from lesions in the stomach, small intestine, and colon. Bleeding is best treated by endoscopic electrocautery or by ablation using laser or argon plasma coagulation.

## DIEULAFOY'S LESION

This vascular abnormality is a rare cause of massive gastrointestinal bleeding, usually from the stomach, but sometimes from the small or large intestine. It is twice as common in men as in women and presents at a mean age of 52 years. This lesion is believed to be present in 1–2% of patients with acute GI hemorrhage.

### Pathology

It is generally accepted that the primary defect in a Dieulafoy's lesion is an abnormally large artery running through the submucosa, or in the some cases the mucosa, of the stomach. The vessel is normal histologically, but does not undergo the normal decrease in caliber as it penetrates from the outer to the inner layers of the stomach. As a result, the "caliber-persistent" vessel is in close contact with the stomach lining and may cause a small erosion in this lining. This can cause the vessel to become eroded, with resultant massive bleeding.

### Clinical Presentation

These lesions typically present with profuse upper GI hemorrhage without symptoms of ulcer disease. The diagnosis can usually be made by endoscopy, and the site of bleeding is usually located within 6 cm of the junction of the esophagus and the stomach. The mortality rate from bleeding has been high in the past but has improved significantly with the advent of therapeutic endoscopy.

### Therapy

Historically, surgery was the only effective way to manage Dieulafoy's lesions, often requiring a wedge resection of the entire area. More recently, emergency endoscopy has been used to localize and treat the actively bleeding site. A variety of techniques can be used to achieve hemostasis, including local injection of vasoconstrictive or sclerosing agents, heater probe, electrocoagulation, and laser or argon plasma coagulation. Most patients (80%) with Dieulafoy's lesions can be managed with endoscopic therapy alone. Rebleeding from these lesions may occur and, therefore, patients should be observed closely following treatment.

## HEMANGIOMA

Hemangiomas are vascular growths that can be found in both the small intestine and the colon. Although rare, they are considered the second most common vascular lesion of the colon (after vascular ectasias). The lesions may be present at birth and enlarge with the normal

development of the child. They may be single or multiple and can be associated with hemangiomas on the skin or in other organs.

### Pathology

Hemangiomas are often small, ranging from a few millimeters to 2 cm, but larger lesions occur, especially in the rectum (see the following discussion on cavernous hemangiomas of the rectum). Hemangiomas can be classified into two distinct histologic types, capillary hemangiomas and cavernous hemangiomas. Capillary hemangiomas are uncommon and may be found in the small intestine and appendix. These reddish-purple lesions are usually solitary and well circumscribed. They are made up of tiny vessels, closely packed together into clusters separated by very little connective tissue. In contrast, cavernous hemangiomas are most often found in the large intestine or rectum and can be quite large, extending up to 20 or 30 cm in length, with enough bulk to encroach on the bowel lumen. They also can be well-circumscribed and polypoid. Histologically, they are seen as numerous dilated, irregular, blood-filled spaces that may extend through the entire wall of the bowel.

### Clinical Presentation

Hemangiomas usually present in young men and women in their second decade. Bleeding is usually slow, producing anemia or rarely black, tarry, or red stools. Cavernous hemangiomas may present with brisk bleeding, and death from exsanguination has occurred. Occasionally, large lesions can present with bowel obstruction. Diagnosis is best made by endoscopy, because X-ray studies, including angiography, frequently are normal. Endoscopically, the lesions appear as bright red spots or nodules (capillary hemangiomas) or as reddish-purple polyps or mounds (cavernous hemangiomas).

### Therapy

Small, solitary hemangiomas can be ablated locally by endoscopic techniques. Most larger lesions must be approached surgically, because even a small endoscopic biopsy can result in massive bleeding or perforation. Either the hemangioma alone or the involved segment of bowel harboring the vascular growth is resected. Alternative therapies have been used in unresectable cases. These include injection of sclerosing agents, freezing methods (cryotherapy), and ablation of the arterial supply to the lesion. In most cases, these techniques have been only marginally successful.

## CAVERNOUS HEMANGIOMA OF THE RECTUM

These lesions are often considered separately from other hemangiomas because of their different presentation and clinical course. They are often solitary and quite extensive in size, involving much of the rectum and occasionally the sigmoid colon as well. Because of their large vascular channels, these lesions may present with massive rectal bleeding. A soft mass may be detected on digital rectal examination. The diagnosis can also often be suggested by clues obtained from plain X rays of the abdomen. These studies may show focal calcific densities (phleboliths), which form in the dilated sinuses, or a distorted rectal air column. Endoscopically, elevated plum-red nodules are seen; ulcers and rectal inflammation may also be present. Local measures to control bleeding are only temporarily effective. Embolization and surgical ligation of major feeding vessels have also been used, but ultimately resection of the rectum may be required.

## BLUE RUBBER BLEB NEVUS SYNDROME

The blue rubber bleb nevus syndrome is a rare disorder that manifests as cavernous hemangiomas on the skin and in the gastrointestinal tract. The descriptive name of this condition derives from the fact that the blue skin lesions have the appearance and feel of rubber nipples.

### Pathology

The lesions are quite distinctive; they are blue and raised, ranging from 0.1 to 10 cm in size, and have a wrinkled surface. A few to several hundred of these lesions can be found on the skin, usually on the trunk, extremities, and face. They are often present at birth or appear during childhood. Microscopically, the lesions are cavernous hemangiomas composed of dilated capillaries.

### Clinical Presentation

Gastrointestinal tract involvement with hemangiomas of the blue rubber bleb nevus syndrome is very common. Lesions can be found throughout the gastrointestinal tract but are most common in the small bowel. They usually present with low-grade gastrointestinal bleeding. The typical presentation is that of a young adult with chronic anemia and the characteristic skin

lesions (characteristic by appearance and by the wrinkled sac they leave on compression).

### Therapy

Although barium and angiographic studies have both been used to diagnose this disorder, endoscopy is the best available modality (although limited in the length of small bowel it can visualize). Conservative treatment with iron supplementation is usually tried in these patients. If bleeding is significant and confined to one or a few segments of bowel, surgical resection of the involved areas may be needed. Endoscopic treatment with laser therapy has been used but may be dangerous if the lesion involves the full thickness of the bowel wall. Endoscopic ultrasound is a new technique that may help define the depth of bowel involvement prior to therapy.

## KLIPPEL–TRENAUNAY–WEBER SYNDROME

This syndrome is characterized by three cardinal features: a large vascular lesion (hemangioma) involving a lower limb, with varicose veins, and enlargement of the bones and soft tissues of, the involved limb. Swelling of the involved leg is very common. This disorder may cause gastrointestinal bleeding from cavernous hemangiomas, usually located in the colon or rectum. Vaginal hemangiomas may also cause significant vaginal bleeding. Bleeding may be mild or heavy and is often recurrent. Surgical resection of the involved area of bowel is standard, but recently endoscopic laser therapy has been tried in several cases with good results.

### See Also the Following Articles

**Hemorrhage • Lower Gastrointestinal Bleeding and Severe Hematochezia • Occult Gastrointestinal Bleeding • Upper Gastrointestinal Bleeding**

### Further Reading

Boley, S. J., and Brandt, L. J. (1986). Vascular ectasias of the colon—1986. *Dig. Dis. Sci.* **31**, 265.

Boley, S. J., Sammartano, R. J., Adams, A., *et al.* (1977). On the nature and etiology of vascular ectasias of the colon: Degenerative lesions of aging. *Gastroenterology* **72**, 650.

GASTROLAB Image Gallery web site. Picture archive. Retrieved at http://www.gastrolab.net/pawelcom.htm.

Guttmacher, A. E., Marchuk, D. A., and White, R. I. (1995). Hereditary hemorrhagic telangiectasia. *N. Engl. J. Med.* **333**, 918.

Jabbari, M., Cherry, R., Lough, J. O., Daly, D. S., Kinnear, D. G., and Goresky, A. (1984). Gastric antral vascular ectasia: "The watermelon stomach." *Gastroenterology* **87**, 1165.

Reinus, J. F., and Brandt, L. J. (1990). Upper and lower gastrointestinal bleeding in the elderly. *Gastroenterol. Clin. North Am.* **19**, 293.

Samuel, M., and Spitz, L. (1995). Klippel Trenaunay syndrome: Clinical features, complications, and management in children. *Br. J. Surg.* **82**, 757.

Stark, M. E., Gostout, C. J., and Balm, R. K. (1992). Clinical features and endoscopic management of Dieulafoy's disease. *Gastrointest. Endoscop.* **38**, 545.

# Vascular Abnormalities, Pediatric

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**Blue Rubber Bleb Nevus syndrome** A disorder consisting of multifocal venous malformations of the skin, soft tissues/muscles, gastrointestinal tract, or almost any organ.

**hemangioma** Benign endothelial tumors.

**hereditary hemorrhagic telangiectasia** Also known as Osler-Weber-Rendu disease, with autosomal dominant inheritance of vascular malformations in multiple organ systems, including the lungs, brain, and gastrointestinal tract.

**Kaposiform hemangioendothelioma** Endothelial hyperplasia, which is less discrete and more aggressive than typical hemangioma. It can be associated with very low platelet counts (known as Kasabach Merritt phenomenon).

**vascular malformation** A result of abnormal development of vascular structures. They are subclassified based on their predominant channel type (capillary, venous, lymphatic, arteriovenous, etc.).

**Skin and soft tissue vascular anomalies are relatively common in infants and children, although visceral vascular anomalies are much less common and often asymptomatic. The nomenclature of vascular anomalies, in general, has been misleading and propagates misconceptions that often lead to incorrect diagnosis and treatment. Nevertheless, most gastrointestinal vascular anomalies have typical clinical presentations, natural histories, and endoscopic and radiologic appearances. An understanding of such patterns of presentation facilitates accurate diagnosis and appropriate management of these uncommon lesions.**

## CLASSIFICATION

Vascular anomalies in childhood are split into two broad categories: tumors and vascular malformations. Imprecise terminology has been inconsistently applied to a variety of vascular anomalies. A reclassification, encompassing clinical behavior, cellular kinetics, and physical appearance, was proposed by Mulliken and Glowaki in 1982 and can also be applied to visceral lesions (Table I). For practical purposes, most of these vascular tumors of childhood are hemangiomas, which are benign endothelial tumors. The descriptors "cavernous" or "capillary" hemangioma are misleading and unnecessary. Often the lesions described as cavernous hemangiomas are in fact vascular malformations rather than true hemangiomas.

TABLE I Biologic Classification of Vascular Anomalies

| Tumors | Malformations |
|---|---|
| **Cause: Endothelial hyperplasia** | **Cause: Dysmorphogenesis with normal endothelial turnover** |
| Hemangioma | Capillary |
| Congenital hemangioma | Venous |
| Kaposiform hemangioendothelioma | Lymphatic |
| Rare forms | Arterial/arteriovenous |
| | Complex-combined |

Vascular malformations result from errors in vascular morphogenesis and are not tumors. They are subdivided into their predominant channel type: capillary, venous, lymphatic, arterial, or a combination of these. The suffix "-oma" in modern medical terminology (e.g., lymphangioma, cystic hygroma, and angioma) often indicates a neoplastic process with up-regulated cell growth. These terms should be avoided because they misrepresent the true biology of the nonneoplastic, quiescent endothelium in vascular malformations.

## HEMANGIOMAS

### Epidemiology and Pathogenesis

Hemangioma is the most common tumor of infancy and childhood. It occurs in 4–10% of white infants and 23% of low-birth-weight premature infants weighing $< 1200$ g. The incidence in dark-skinned babies is low. Most hemangiomas are single, but 20% of affected infants have multiple lesions. Multiple cutaneous tumors (more than 5) often arise in association with visceral lesions [mostly in the liver, gastrointestinal (GI) tract, lungs, and brain]. Hemangiomas occur with a female to male ratio of 3 : 1 to 5 : 1. This ratio is higher in problematic tumors and in rare cases where there are associated structural anomalies. There is also evidence suggesting that the risk of hemangioma is significantly higher in offspring of women who undergo chorionic villus sampling.

 

The triggers for hemangiogenesis are not entirely clear, although there are hypotheses suggesting a viral cause, such as human parapox virus infection or genetic alteration. In a study of monozygotic versus dizygotic twins, there was no strong evidence for Mendelian inheritance; however, there are rare kindreds that suggest familial transmission in an autosomal dominant pattern with incomplete penetrance and variable expressivity. A putative locus on 5q has been identified in three families with coexistence of hemangioma and vascular malformation. The median age for the appearance of most cutaneous hemangiomas is 2 weeks after birth (Fig. 1). However, approximately one-third to one-half are nascent at birth. Hemangiomas evolve through three stages:

1. Proliferation (usually between 0 and 1 year of age), characterized by up-regulation of two potent angiogenic peptides, vascular endothelial growth factor and basic fibroblast growth factor.
2. The involuting phase (usually between 1 and 7 years of age), characterized by a higher rate of apoptosis than mitosis, with decreased interferon-β in the overlying epidermis. The rate of regression is unrelated to the appearance, site, size of tumor, or the gender of the patient. Involution is complete in 50% of children by 5 years and in 70% by 7 years of age, with gradual improvement until 10–12 years of age.
3. The involuted phase (after 7 years of age), in which the hemangioma may be completely invisible, leave a pale fibrofatty residuum, or lead to some fine telangiectatic vessels on the overlying skin. Lesions that have ulcerated during proliferation leave a scar.

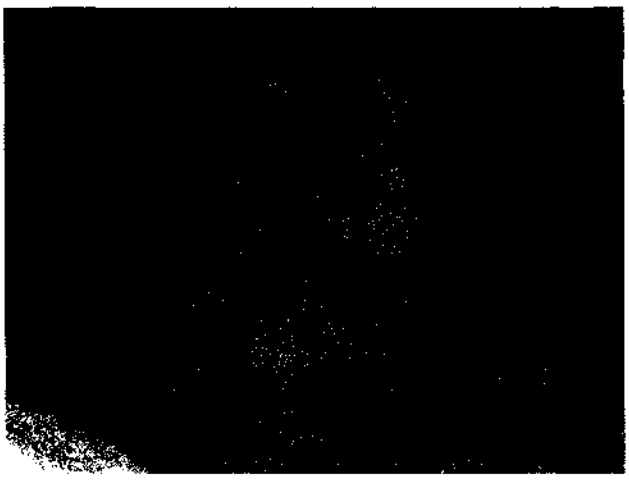

FIGURE 1 Typical cutaneous hemangioma.

## Clinical Manifestations

Hemangiomatosis refers to multiple cutaneous and visceral hemangiomas. The liver is the most common visceral site involved and can range in presentation from tiny, asymptomatic tumors found incidentally, to large, single or multiple tumors, with or without cardiac complications. These typically manifest in the first 4 months of life with hepatomegaly, anemia, and high-output cardiac failure. Abdominal compartment syndrome can occur when the hepatomegaly is so marked that it limits diaphragmatic excursion and venous return to the inferior vena cava, resulting in respiratory and renal failure. Occasionally, the liver hemagioma may invade directly into the duodenum or colon or parasitize its blood supply. Symptomatic hemangiomas of the stomach, small bowel, and colon are rare. When detected, they often exhibit diffuse, patchy involvement and they are also often associated with multifocal cutaneous lesions.

## Radiologic Features

Any infant with more than five cutaneous hemagiomas should be considered for screening by ultrasound and/or magnetic resonance imaging (MRI) to evaluate for possible lesions in the liver. Doppler ultrasound of the liver sometimes detects a liver hemangioma in its early proliferative phase; lesions may even be detected on antenatal ultrasound. The ultrasound can show single or multiple lesions with decreased arterial resistance, increased venous velocity, and discrete soft tissue mass. Sonography is useful in documenting tumor response to pharmacologic therapy. On MRI, hemangiomas appear to be solid tissue of intermediate intensity on T1 images and moderate hyperintensity on T2 images. Flow voids are indicators of shunting (rapid flow) between feeding arteries and dilated draining veins and are prominent around and within the tumor. One should be aware that because both intrahepatic hemangioma and arteriovenous malformations (AVMs) are fast flow, they can often be mistaken for one another. Finally, radionuclide scanning with technetium Tc-99m-tagged red blood cells can be used to document deep multiple hemangiomas in the GI tract.

## Treatment

Most lesions require no treatment. However, if there is a threat to life, limb, vital function, or significant tissues, the lesions should be treated pharmacologically. The first-line agent is oral prednisone, 2–3 mg/kg/day (up to 5 mg/kg/day for refractory lesions) for 1 m ith, followed by a slow taper over the s

5–7 months. Rebound growth after weaning the dose is a common phenomenon and the dose may need to be temporarily increased. Small focal lesions can be treated with sequential intralesional injections of triamcinolone. Approximately one-third of treated lesions undergo rapid involution, one-third stabilize, and one-third have no response. The growth of the lesions is inhibited, probably from the mild antiangiogenic effect of corticosteroids.

For steroid-resistant lesions, treatment with a more potent angiogenesis inhibitor, interferon α-2b, 2–3 million units/$m^2$/day, can be given subcutaneously. The response is typically slower, although most lesions respond. Side effects include a low-grade fever in the first 1–2 weeks (which can be minimized by pretreatment with acetominophen), transient transaminase elevation, neutropenia, and anemia (usually mild and not requiring discontinuation of the interferon). The last and potentially most serious side effect is spastic diplegia, which has been reported in approximately 5% of infants treated with interferon.

Gastrointestinal hemangiomas are rare and can be single, multifocal, or diffuse infiltrative tumors. Bleeding may occur and necessitate repeated transfusions. On occasion, focal lesions can be treated with local endoscopic (band ligation, argon plasma coagulation, or intralesional corticosteroid injection) or surgical techniques (enterotomy). However, one cannot always be assured that any endoscopically visualized lesion is the only bleeding site, as there may be other lesions out of reach of the endoscope or colonoscope. In the case of diffuse infiltrative hemangioma(s) with life-threatening hemorrhage, management consists of supportive care with repeated transfusions, parenteral nutrition, and antiangiogenic therapy (to accelerate involution), rather than surgical resection (as this is usually not possible).

For relatively small, asymptomatic, hepatic lesions, sequential physical exam and ultrasound are typical management. Therapy is typically reserved until there is significant hepatomegaly or symptoms such as congestive heart failure. Initial therapy is with systemic steroids and second-line therapy is interferon. If symptoms worsen or persist, hepatic arteriography may be considered. Embolization is a potential therapy, only if there are direct macrovascular shunts through the lesion(s). Chemotherapy with cyclophosphamide or vincristine has also occasionally been effective for life-endangering hepatic hemangiomas. Endoscopic evaluation is not typically needed, but may be useful in cases where there is concern about the liver hemangioma invading the bowel or its vascular supply. Endoscopy may be indicated to confirm and localize the lesion(s), but it is unlikely to be sufficient for hemostasis of gastrointestinal bleeding if it occurs. Surgical resection of liver hemangiomas is almost never indicated. Liver transplant is considered only in rare instances when the tumor is unresponsive to the aforementioned therapies and the patient is in extremis from abdominal compartment syndrome. In cases of such large lesions, it is crucial to screen for acquired hypothyroidism, as some hemangiomas have been demonstrated to express type 3 iodothyronine deiodinase, which inactivates circulating thyroid hormone. Prior screening for congenital hypothyroidism is generally normal in these individuals and a normal early thyroid-stimulating hormone does not ensure that hypothyroidism will not develop as a hemangioma enlarges. Thus, repeated testing should be performed if the lesion undergoes significant growth.

Congenital hemangioma is a rare variant in which a lesion is fully grown at birth and involutes rapidly, usually by 1 year of age. No congenital hemangioma has been reported in the gastrointestinal tract.

## KAPOSIFORM HEMANGIOENDOTHELIOMAS

Kaposiform hemangioendotheliomas (KHEs) are generally much more aggressive than hemangiomas, although they follow a similar pattern of spontaneous involution. They are much less discrete and tend to blend in diffusely with the surrounding structures. Both sexes are equally affected. Although involvement in a hollow viscus has not been reported, the torso, retroperitoneal structures, and liver may be involved. Kasabach-Merritt phenomenon occurs in association with these lesions and is characterized by a severe thrombocytopenia (typically 2000 to 5000 platelets/$mm^3$), which places the infant at risk for hemorrhage in various sites, including the gastrointestinal tract. KHE is clearly differentiated from common hemangioma via MRI; KHEs have a poorly defined tumor margin, extend across tissues, and have relatively small vessels. Biopsy is rarely indicated for a coagulopathic tumor and it is usually too diffusely infiltrative and large to resect. In contrast to hemangiomas, interferon has been effective only in 50% of infants and no single pharmacologic therapy has proven to be consistently effective. Two caveats must be remembered in managing thrombocytopenia in these lesions: Platelet transfusion should be avoided unless there is active bleeding or a surgical procedure is indicated. Heparin should not be given, as it can stimulate tumor growth, platelet trapping, and worsened bleeding.

## VASCULAR MALFORMATIONS

### Capillary Malformations

Capillary malformations are composed of dilated capillary to venular sized vessels, with a paucity of normal nerve fibers around these vessels on immunohistochemical staining. In the skin, they include port wine stains and telangiectasias. It is extremely rare to have symptomatic capillary malformations of the viscera. Hereditary hemorrhagic telangiectasia (HHT), also known as Osler–Weber–Rendu disease, can present with nosebleeds, shunting through pulmonary arteriovenous malformations, cerebral lesions, and potential gastrointestinal mucosal lesions. The pulmonary complications are usually apparent before the GI manifestations, and if GI bleeding occurs, it is rare before adulthood. There are rare case reports of HHT associated with juvenile polyps, which are highly vascular and a common source of bleeding during childhood. In these cases, the child may present with gastrointestinal bleeding from the polyps rather than the vascular anomaly.

### Venous Malformations

Venous malformations are the most common symptomatic vascular anomaly of the GI tract in childhood. Most patients have only single lesions, though some have multiple malformations. Most of these malformations are sporadic, although genes for several rare, autosomal dominant forms have been identified. They have a wide range in size (miniscule to massive) and shape (flat to bulky and amorphous). Grossly, they are nonpulsatile, appear deep purple, decompress with manual pressure, and refill shortly after release (Fig. 2). Microscopically, they are channels lined by endothelium but lack smooth muscle. They have also been improperly termed cavernous hemangiomas because of their soft, spongy feel and color. However, this term should not be used because these lesions are not tumors, do not involute, and do not respond to pharmacologic treatment. Venous malformations of the skin and soft tissue are often asymptomatic, other than being unsightly and sometimes disfiguring. Blood can stagnate in the nonlaminar channels and cause a local consumptive coagulopathy. Thrombosis may occur, resulting in sudden swelling, firmness, and pain. In large lesions, systemic hypofibrinogenemia and prolonged prothrombin time may result from factor consumption. Thrombocytopenia is atypical. Even without frank thrombus, pain can occur due to congestion or low-grade thrombosis. Small, palpable phleboliths can form and appear as radiopaque spherical densities on radiographic studies. If present, these

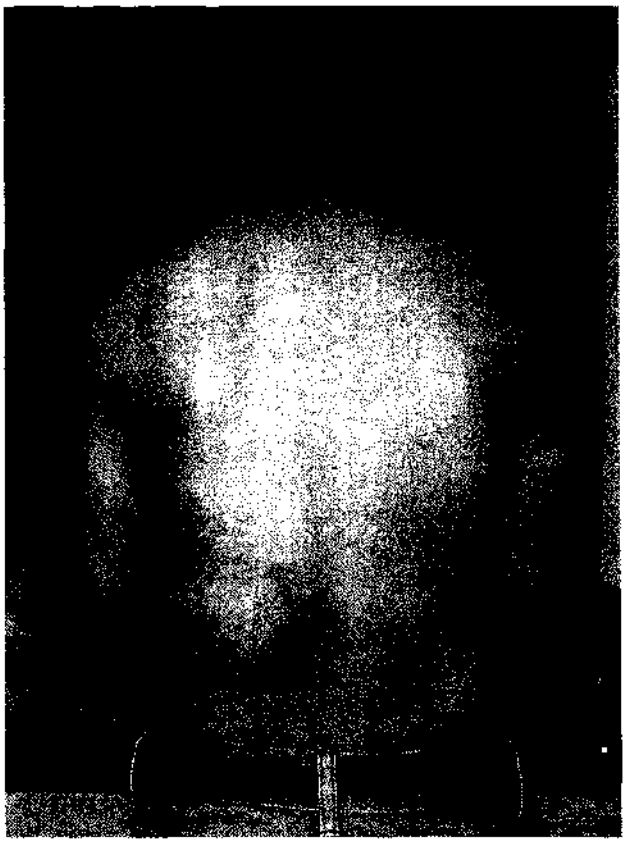

**FIGURE 2** Typical cutaneous venous malformation.

serve as an easy distinguishing feature of venous malformations from hemangiomas. In the GI tract, they most commonly present with upper or lower, acute or chronic, gastrointestinal bleeding. Since GI bleeding is not common in childhood, it is often not suspected or identified until the patient is found to be profoundly anemic. This is highlighted by the fact that children independent in toileting may not report a change in bowel habits and if parents notice dark-colored stools, they may not appreciate their significance. Pain and obstruction are less common presenting symptoms of venous malformations in the gut. They are common in the liver and spleen (often improperly termed hemangiomas) and usually asymptomatic.

A single, focal venous malformation can occur anywhere in the gastrointestinal tract, vary in size ($< 1$ cm to $> 20$ cm diameter), and can be mucosal, mural, or transmural (Fig. 3). Endoscopic ultrasound can be used to determine the depth of mural involvement, although the entire lesion must be viewed, as there can be varying depths of involvement in different parts of the same lesion. Therapeutic endoscopic procedures should be performed only on superficial lesions and surgical backup should be available for complications that may

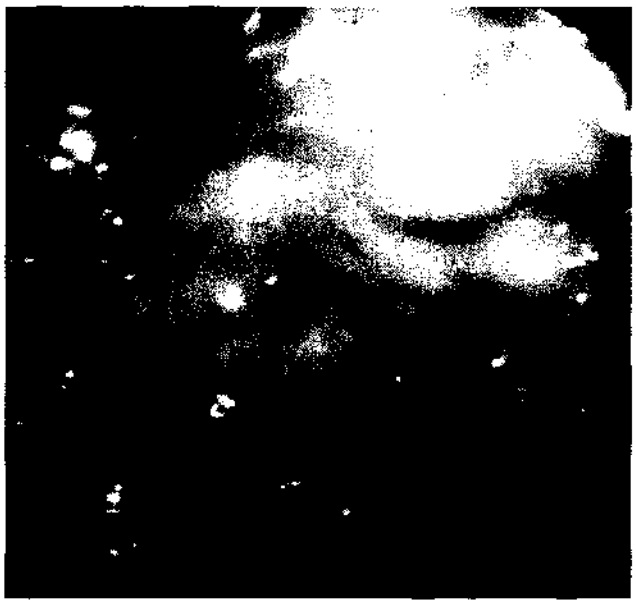

FIGURE 3 Endoscopic appearance of colonic venous malformation.

arise. Small, muscosal lesions can be eradicated with endoscopic band ligation. If the lesion is not transmural, endoscopic sclerotherapy may also be used, but is unlikely to be sufficient treatment of large lesions. Potential complications include perforation (if unsuspected transmural lesions are treated endoscopically) and intravascular migration of sclerosing material from large lesions (if there are anomalous or large vessels communicating with the lesion). In such cases, pretreatment angiography or intralesional injection of contrast under fluoroscopy may be helpful. Surgical excision is needed to eradicate large or transmural venous malformations.

Blue Rubber Bleb Nevus syndrome (BRBNS) consists of multifocal venous malformations of the skin, soft tissues/muscles, gastrointestinal tract, or almost any organ. Skin lesions vary in size (usually 3–15 mm), are deep blue or purple in color, are flat or minimally raised, may be tender to palpation, and have a predilection for the trunk, palms, and soles (Fig. 4). A total body survey with delayed imaging of Tc-99m-labeled red blood cells or scintigraphy using single-photon emission computed tomography (for a three-dimensional picture) shows pooling of the labeled cells within the lesions. Almost all patients have multiple lesions within the liver. Gastrointestinal lesions have an endoscopically pathognomonic appearance: discrete, purple berry-like protuberances, several millimeters to centimeters in size, scattered from mouth to anus (Figs. 5 and 6). Most are broad-based, but some have a narrow pedicle. Typically, there is a broad rim of normal mucosa encircling the base and extending up to the reddish blue apex of the lesion, although normal mucosa may also cover the entire mass. Affected patients present from early infancy to young adulthood, invariably with chronic GI bleeding (usually consistent black stools rather than acute hemorrhage) and anemia. Most patients require chronic transfusions, iron replacement, and erythropoietin. Some patients can also present with intussusceptions or volvulus. Single pharmacologic or endoscopic treatment studies to date have not yielded reproducible, durable efficacy. Therapies that have been evaluated include interferon-$\alpha$, somatostatin, high-dose intravenous gammaglobulin, sclerotherapy, band ligation, and laser photocoagulation. Because most lesions are generally in the unexamined portions of the small intestine, endoscopic therapy alone is unlikely to decrease a patient's transfusion requirement. There is one report of endoscopic polypectomy with laparoscopic assistance to approach small bowel lesions. The authors' approach to BRBNS is to eradicate all hollow viscus venous malformations using a combined endoscopic and operative approach when a patient requires repeated transfusions or has refractory severe anemia. Since BRBNS lesions are congenital, present at birth (though they may be minute), and expand over time, operation is delayed until bleeding is significant, in hopes that all lesions are "ripe" and can all be eradicated in one procedure. Lesions are identified endoscopically in the esophagus to duodenum and rectum to colon. If lesions are superficial, endoscopic band ligation is performed. Otherwise, they are surgically excised. Small bowel lesions are identified via enteroscopy through

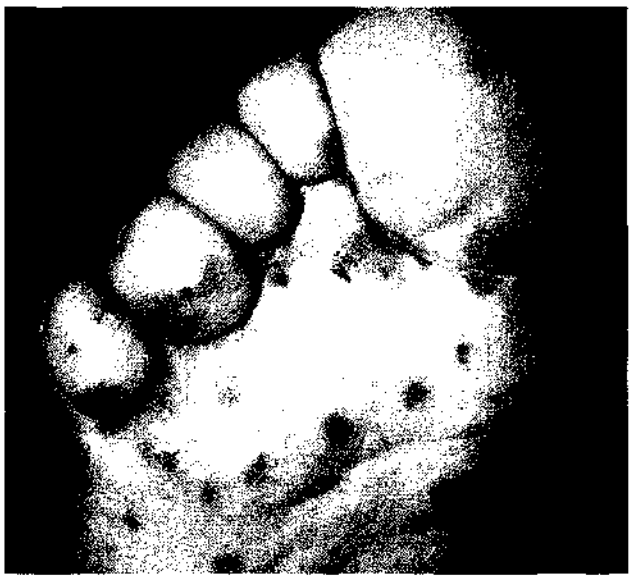

FIGURE 4 Skin lesions of the Blue Rubber Bleb Nevus syndrome.

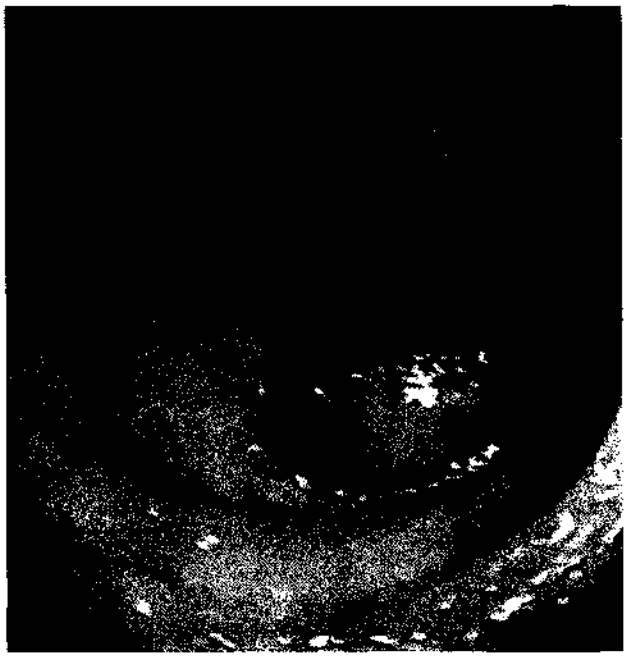

**FIGURE 5** Endoscopic appearance of venous malformations of the Blue Rubber Bleb Nevus syndrome.

enterotomies or by inversion of segments of intestine by sequential intussusceptions through multiple enterotomies. Small bowel length is preserved by wedge excision or ligation of lesions rather than circumferential small bowel resections. Outcomes have been excellent.

Diffuse venous malformations involve large contiguous sections of bowel and extraintestinal structures (such as mesentery, retroperitoneum, pelvis, muscles, subcutaneous tissues, and skin). Upper visceral diffuse venous malformations may involve the mesenteric, splenic, and portal veins. If the portal vein is anomalous, one should investigate for presinusoidal hypertension. These lesions may be untreatable, although portal decompression can be helpful by decreasing intralumenal pressure of the malformation.

Lower visceral diffuse venous malformations can extend from the anorectum proximally. They usually are transmural and extend into the pelvis. They may involve the entire colon or just the left side. Imaging studies demonstrate a markedly thickened colon and anorectum with or without phleboliths. Colonoscopy reveals a massively engorged, purple mucosa with contiguous varix-like projections, which can cause chronic bleeding requiring life-long, repeated transfusions. However, endoscopic therapy is futile in all cases and may exacerbate the bleeding. Surgery can involve partial colectomy with end colostomy or colectomy with anorectal mucosectomy and endorectal coloanal or ileoanal pull-through. Full-thickness rectal resection should be avoided because there can be uncontrollable hemorrhage from the extrarectal pelvic venous malformation.

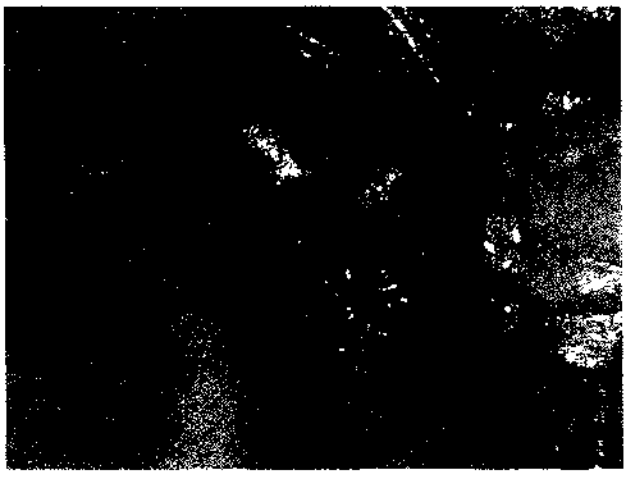

**FIGURE 6** Intestinal lesions of the Blue Rubber Bleb Nevus syndrome.

### Arteriovenous Malformations

AVMs are high-flow lesions between abnormal arteries and veins via many anomalous communications, without a normal intervening capillary bed. True AVMs of the GI tract are rare and many so-named lesions are in fact venous malformations. Endoscopically, AVMs in the gut appear pulsatile and demonstrate high flow on endoscopic ultrasound. Embolization of GI AVMs generally results in necrosis and perforation. Thus, surgical resection is the only curative therapy for gut lesions and presurgical localization may be performed by tattooing during selective arteriography.

### Lymphatic Malformations

Lymphatic malformations of the GI tract are uncommon and mesenteric cysts may represent lymphatic malformations of the lacteals. Protein-losing enteropathy and ascites may be seen in association with anomalous development of the mesenteric lymphatics, cisterna chili, and thoracic duct. Endoscopy is of limited use in diagnosis and therapy.

### Complex Combined Vascular Malformations

Complex combined vascular malformations result from various combinations of anomalous vessel channel types. The most common form in the GI tract is the capillary–lymphaticovenous malformation of the Klippel–Trenaunay syndrome (Fig. 7). This syndrome is characterized by an enlarged lower extremity at birth,

FIGURE 7 Klippel–Trenaunay syndrome.

a massive distorted foot, and axial overgrowth. Purple capillary stains are usually prominent and lymphatic vesicles protrude through the skin. Extension of the lesion into the pelvis to involve the bowel and bladder is not uncommon, though some with Klippel–Trenaunay syndrome may have no GI symptoms. On colonoscopy, the appearance of lesions is varied, sometimes with diffuse purple vascular discoloration and varied degrees of mural thickening. Therapy is indicated only for bleeding resulting in severe chronic anemia or if there is recurrent cellulitis of the buttock or thigh. These infections are often demonstrated to result from enteric organisms that translocate directly through the abnormal mucosal barrier in the malformation. Therapy may entail partial colectomy with diverting colostomy or colectomy with anorectal mucosectomy and coloanal endorectal pull-through.

An appreciation of clinical patterns, accurate nomenclature, associated visible cutaneous lesions, endoscopic appearances, and radiologic findings is important in the proper diagnosis and treatment of vascular anomalies of the gastrointestinal tract.

## See Also the Following Articles

Kaposi's Sarcoma • Vascular Abnormalities

## Further Reading

Fishman, S. J., Burrows, P. E., Leichtner, A. M., *et al.* (1998). Gastrointestinal manifestations of vascular anomalies in childhood: Varied etiologies require multiple therapeutic modalities. *J. Pediatr. Surg.* 33, 1163.

Fishman, S. J., and Fox, V. L. (2001). Visceral vascular anomalies. *Gastrointest. Endosc. Clin. North Am.* 11, 813–834.

Fishman, S. J., Shamberger, R. C., Fox, V. L., and Burrows, P. E. (2000). Endorectal pull-through abates gastrointestinal hemorrhage from colorectal venous malformations. *J. Pediatr. Surg.* 35, 982–984.

Marler, J. J., Fishman, S. J., Upton, J., Burrows, P. E., Paltiel, H. J., Jennings, R. W., and Mulliken, J. B. (2002). Prenatal diagnosis of vascular anomalies. *J. Pediatr. Surg.* 37, 318–326.

Mulliken, J. B., Fishman, S. J., and Burrows, P. E. (2000). Vascular anomalies. *Curr. Prob. Surg.* 37, 517–584.

Vascular Anomalies Center Website. Available at http://www.childrenshospital.org/vascularanomalies/.

# Vasculitis

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antineutrophil cytoplasmic antibodies Proteins directed against cytoplasmic neutrophil antigens such as proteinase 3 and myeloperoxidase; useful in the diagnosis of small-vessel vasculitis.

Janeway lesion Painless, macular lesions on the palms and soles, characteristic of infective endocarditis.

oligoarthritis Form of arthritis that involves more than one but a relatively small number of joints.

Osler node A tender, raised, cutaneous lesion, typically on the finger pads; characteristic of infective endocarditis.

**Vasculitis is defined pathologically as a vessel wall lesion characterized by the presence of leukocytes, with reactive damage to mural vascular structures resulting in tissue** ischemia and necrosis. Clinically, vasculitis refers to **syndromes resulting from such local, regional, or systemic inflammation and necrosis of blood vessels. Vasculitis may occur in the context of a well-defined disease such as infective endocarditis (secondary vasculitis) or** may be idiopathic. Secondary vasculitis is much more **common than idiopathic vasculitis. Disorders that mimic clinical vasculitis include multiple cholesterol emboli syndrome and several occlusive vasculopathic disorders. Histologically, such disorders are notable for the absence of vasculitic changes. The term "vasculopathy" is often applied to such disorders.**

## CLASSIFICATION

The idiopathic or primary systemic vasculitides are a heterogeneous group of diseases with frequent clinical and pathologic overlap. Classification is based on vessel size, clinical features, and histology (Table 1). Three main categories are recognized based on vessel size (large, medium, and small) and are further subclassified based on clinical and histologic characteristics.

## EPIDEMIOLOGY

Although the causes of vasculitis are largely unknown, epidemiologic data have suggested roles for geographic, genetic, and environmental factors. Giant cell arteritis is the most common vasculitis in older individuals from North America and Europe. Takayasu's arteritis is predominantly seen in individuals from the Far East and Southeast Asia. The medium- and small-vessel vasculitides (polyarteritis nodosa and microscopic polyangiitis, Wegener's granulomatosis, and Churg–Strauss syndrome) are all relatively uncommon. Kawasaki disease primarily occurs in children under the age of 5 years. Henoch–Schönlein purpura is the most common type of vasculitis in children and is relatively infrequent in adults. Cutaneous leukocytoclastic vasculitis is relatively common and frequently seems to be precipitated by the use of medications.

## ETIOLOGY AND PATHOGENESIS

The systemic vasculitides are immune-mediated inflammatory diseases for which the precise etiology is unclear. These diseases may be triggered by infection, with the release of proinflammatory cytokines and up-regulation of leukocyte adhesion molecules in an uncontrolled manner. Several factors appear to determine the size of vessel involved, the subsequent inflammatory responses, and systemic manifestations. These include the nature of the antigen involved, factors modulating endothelial cell activation, and other components of the inflammatory cascades, including cytokines, costimulatory molecules, and intracellular activation pathways. The end result is disruption of vessel integrity, producing clinical signs and symptoms of tissue ischemia.

Giant cell arteritis appears to be a T-cell-mediated disease. Macrophages produce interleukin-1, interleukin-6, and transforming growth factor-β and often become organized as multinucleated giant cells under the influence of interferon γ. Takayasu's arteritis is also a granulomatous polyarteritis in which CD8 T cells have been identified as the major cell type. Several candidate organisms have been associated with Kawasaki syndrome. It is speculated that toxins may act as superantigens. Polyarteritis nodosa is an immune complex vasculitis and has been reported in association with hepatitis B virus in some cases. Wegener's granulomatosis, microscopic polyangiitis, and Churg–Strauss syndrome have been referred to as the antineutrophil

 

TABLE I Names and Definitions of Vasculitides Adopted by The Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis[a]

| Name | Definition |
|---|---|
| **Large-vessel vasculitis** | Giant cell (temporal) arteritis<br>Granulomatous arteritis of the aorta and its major branches with a predilection for the extracranial branches of the carotid artery; often involves the temporal artery; usually occurs in patients older than 50 years and often is associated with polymyalgia rheumatica |
| | Takayasu arteritis<br>Granulomatous inflammation of the aorta and its major branches; usually in patients younger than 50 years |
| **Medium-vessel vasculitis** | Polyarteritis nodosa (classic polyarteritis nodosa)<br>Necrotizing inflammation of medium or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules |
| | Kawasaki disease<br>Arteritis of large, medium, and small arteries associated with the mucocutaneous lymph node syndrome; coronary arteries are often involved and aorta and veins may be involved; usually occurs in children |
| **Small-vessel vasculitis** | Wegener's granulomatosis<br>Granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels (e.g., capillaries, venules, arterioles, and arteries); necrotizing glomerulonephritis is common |
| | Churg–Strauss syndrome<br>Eosinophil-rich and granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels; associated with asthma and eosinophilia |
| | Microscopic polyangiitis (microscopic polyarteritis)<br>Necrotizing vasculitis, with few or no immune deposits, affecting small vessels (i.e., capillaries, venules, or arterioles); necrotizing arteritis involving small and medium-sized arteries may be present; necrotizing glomerulonephritis is very common and pulmonary capillaritis often occurs |
| | Henoch–Schönlein purpura<br>Vasculitis, with IgA-dominant immune deposits, affecting small vessels (i.e., capillaries, venules, or arterioles); typically involves skin, gut, and glomeruli, and is associated with arthralgias or arthritis |
| | Essential cryoglobulinemic vasculitis<br>Vasculitis, with cryoglobulin deposits, affecting small vessels (i.e., capillaries, venules, or arterioles), and associated with cryoglobulins in serum; skin and glomeruli are often involved |
| | Cutaneous leukocytoclastic vasculitis or glomerulonephritis<br>Isolated cutaneous leukocytoclastic angiitis without systemic vasculitis |

[a] Modified from Jennette *et al.* (1994).

cytoplasmic antibody (ANCA)-associated vasculitides. It is thought that the ANCAs play a direct pathogenic role in these disorders. Henoch–Schönlein purpura is an immune complex vasculitis in which immunoglobulin A (IgA) is the principal component. Leukocytoclastic vasculitis results from immune complex deposition in postcapillary venules.

## CLINICAL FEATURES

### General

The systemic vasculitides are inflammatory diseases that often result in simultaneous tissue ischemia of several organ systems. The associated systemic inflammatory response is often clinically evident as fever, weight loss, and malaise. Giant cell arteritis may present as a fever of unknown origin in the elderly.

### Cutaneous

Leukocytoclastic vasculitis is a reaction pattern that may be seen in a variety of vasculitides. When the skin is the only organ system involved, the term "cutaneous leukocytoclastic vasculitis" is assigned. Henoch–Schönlein purpura typically manifests as palpable purpura over the lower extremities. Many other vasculitides can also produce similar lesions. In addition to leukocytoclastic vasculitis, other cutaneous patterns of injury include nodules, ulceration, and bullous lesions. Occasionally, digital gangrene occurs from medium-vessel occlusion. Secondary vasculitides (including cryoglobulinemic vasculitis and immune complex vasculitis from infections such as infective endocarditis) also have prominent cutaneous features. Cryoglobulinemic vasculitis can cause purpura and infarcts of cool peripheral structures such as the digits, ear lobes, and tip of the nose and the penis. Characteristic cutaneous lesions from infective endocarditis are referred to as Osler's nodes and Janeway lesions. Splinterlike hemorrhages in the nail bed are also frequently noted in this disorder.

### Musculoskeletal

Arthritis is a relatively infrequent in the systemic vasculitides. It may involve both large and small joints. Common patterns include a symmetric small-joint synovitis of the upper extremities (as can occur in giant cell arteritis) or an asymmetric oligoarthritis of the large joints (as may occur in the ANCA-associated vasculitides). Muscle involvement may occur in polyarteritis nodosa, presenting as myalgia or muscle weakness.

### Renal

Glomerulonephritis is characteristic of the ANCA-associated small-vessel vasculitides. It is nearly universal in microscopic polyangiitis, very frequent in Wegener's granulomatosis, and can occasionally occur in Churg–Strauss syndrome. It is also frequently seen in Henoch–Schönlein purpura and in cryoglobulinemic vasculitis. Clinical manifestations include hematuria, proteinuria, rapidly progressive glomerulonephritis, acute nephritic syndrome, and occasionally the nephrotic syndrome. Hematuria and mild renal insufficiency are characteristic of Henoch–Schönlein purpura, whereas rapidly progressive glomerulonephritis with moderate to severe renal insufficiency frequently occurs in Wegener's granulomatosis and microscopic polyangiitis. Polyarteritis nodosa causes a renal arteritis without glomerulonephritis. Clinically, this presents with renal insufficiency, hypertension, and proteinuria.

### Gastrointestinal

Gastrointestinal involvement occurs primarily with polyarteritis nodosa and Henoch–Schönlein purpura. Polyarteritis nodosa frequently involves the mesenteric vasculature and can cause bowel infarction, ulceration, and bleeding. Involvement of the pancreatic vessels can cause acute pancreatitis. It may present as postprandial periumbilical pain. Rupture of the mesenteric microaneurysms is a life-threatening complication of polyarteritis nodosa. Localized polyarteritis nodosa is not uncommonly reported in pathologic specimens from patients with acute cholecystitis or appendicitis. Liver inflammation (hepatitis) is an uncommon feature of idiopathic systemic vasculitis and, when prominent, should suggest a secondary infectious cause of vasculitis such as hepatitis C virus, with cryoglobulinemic vasculitis, and the rickettsial diseases. In children, Henoch–Schönlein purpura frequently presents with colicky abdominal pain and gastrointestinal hemorrhage. Some patients experience nausea and vomiting. Hepatomegaly, hydrops of the gallbladder, diarrhea, and pancreatitis have all been reported in Kawasaki syndrome.

### Neurologic

Vasculitis of the central nervous system can occur as an isolated disorder. It is referred to as primary angiitis of the central nervous system. In giant cell arteritis, headache from temporal artery involvement and blindness from central retinal artery ischemia are relatively common. Takayasu's arteritis may present with cerebral ischemia. Vasculitis associated with connective tissue diseases such as systemic lupus erythematosus and

Sjogren's syndrome can also involve the central nervous system. Other systemic vasculitides more commonly involve the peripheral nervous system, often presenting as mononeuritis multiplex with acute foot drop or wrist drop. This is particularly characteristic of polyarteritis nodosa and Churg–Strauss syndrome.

### Pulmonary

Involvement of the upper airway is characteristic of Wegener's granulomatosis, which can involve the nasal septum, ears, larynx, and trachea. Subglottic stenosis is a common complication. Pulmonary infiltrates, nodules, and cavitary lesions are also frequently noted in Wegener's granulomatosis. Pulmonary capillaritis presenting as alveolar hemorrhage is characteristic of microscopic polyangiitis but can also occur with Wegener's granulomatosis. Churg–Strauss syndrome is characterized by asthma. Pulmonary involvement with polyarteritis nodosa is distinctly uncommon. Giant cell arteritis may present with throat pain and cough.

### Other

Kawasaki disease characteristically involves the coronary arteries and, untreated, can result in coronary artery aneurysms. Epididymo-orchitis can occur in polyarteritis nodosa. Eosinophilia is universal in Churg–Strauss syndrome. Ocular manifestations in the systemic vasculitides include scleritis, uveitis, retinal vasculitis, and orbital pseudotumors. Ocular disease is particularly common in Wegener's granulomatosis and giant cell arteritis.

## DIAGNOSIS

The diagnosis of systemic vasculitis is considered when patients present with the systemic inflammatory disorder associated with rapidly progressive multiorgan dysfunction. Certain clinical features are very suggestive of vasculitis. These include acute renal insufficiency with an active urinary sediment, mononeuritis multiplex, unexplained central nervous system ischemia, palpable purpura, and acute pulmonary hemorrhage. In all such cases, it is important to first consider the secondary causes of vasculitis. These include a variety of infectious diseases (such as infective endocarditis, rickettsial diseases, hepatitis C virus infection, and human immunodeficiency virus infection), lymphoproliferative disorders (especially hairy cell leukemia), left atrial myxoma, and drugs such as ergot alkaloids and cocaine. Diagnostic tests that are helpful include those that exclude the secondary causes (blood cultures, viral serology, echocardiography, and urine drug screen) and those that suggest immune complex formation (rheumatoid factor and antinuclear antibody) or the production of antineutrophil cytoplasmic antibodies. ANCA testing is particularly valuable when small-vessel vasculitis presents as a pulmonary–renal syndrome. Indirect immunofluorescence reveals two characteristic patterns: diffuse cytoplasmic immunofluorescence (c-ANCA) is moderately sensitive and specific for active Wegener's granulomatosis, and perinuclear immunofluorescence (p-ANCA) is indicative of microscopic polyangiitis. Most patients with Wegener's granulomatosis will test positive for antiproteinase 3 antibodies by enzyme-linked immunosorbent assay (ELISA) and the majority of patients with microscopic polyangiitis will test positive for antimyeloperoxidase antibodies (anti-MPOs) by ELISA. ANCA titers may fluctuate with disease activity and may predict relapse in Wegener's granulomatosis.

It is important to stress that vasculitis is a pathological diagnosis and every attempt should be made to obtain a tissue diagnosis. Angiography can be useful when obtaining tissue is not feasible (e.g., suspected mesenteric or intracranial vasculitis).

## THERAPY AND PROGNOSIS

Aggressiveness of therapy of the systemic vasculitides is determined by the site, extent, and pace of organ involvement. Drug-induced leukocytoclastic vasculitis is generally a self-limited disease once the offending medication is withdrawn. Occasionally, a short course of oral corticosteroids is necessary. Similarly, Henoch–Schönlein purpura may resolve spontaneously in the absence of any specific treatment. However, if renal involvement is present, therapy is usually indicated. Some vasculitides, such as giant cell arteritis, usually respond to corticosteroids alone. Diseases such as polyarteritis nodosa and Wegener's granulomatosis typically pose a threat of catastrophic organ damage and are usually treated with simultaneous administration of corticosteroids and cytotoxic agents. Once remission is obtained, corticosteroids are the first to be withdrawn followed by the withdrawal of cytotoxic agents. In Wegener's granulomatosis, the ANCA titers fall with remission and may even revert to negative. In some cases, a rising ANCA titer predicts clinical relapse.

Early mortality in the vasculitides is usually from the disease or is the result of complications of acute immunosuppression. Late mortality usually occurs from complications of therapy. The prognosis in leukocytoclastic vasculitis and giant cell arteritis is excellent, whereas diseases such as polyarteritis nodosa and Wegener's

granulomatosis can cause serious morbidity and decreased life expectancy. The 5-year survival of polyarteritis nodosa is 60% and that of Wegener's granulomatosis is 70%.

## See Also the Following Articles

**Henoch–Schönlein Purpura • Hepatitis C • Kawasaki Syndrome**

## Further Reading


Calabrese, L. H., Duna, G. F., and Lie, J. T. (1997). Vasculitis in the central nervous system. *Arthritis Rheum.* 40, 1189.

Fauci, A., Katz, P., Haynes, B., *et al.* (1979). Cyclophosphamide therapy of severe systemic necrotizing vasculitis. *N. Engl. J. Med.* 301, 235.

Freeman, A. F., and Shulman, S. T. (2001) Recent developments in Kawasaki disease. *Curr. Opin. Infect. Dis.* 14(3), 357–361.

Guillevin, L., Le Thi Hong, D., Godeau, P., *et al.* (1988). Clinical findings and prognosis of polyarteritis nodosa and Churg–Strauss angiitis: A study in 165 patients. *Br. J. Rheumatol.* 27, 258.

Jennette, J. C., and Falk, R. J. (1997). Small-vessel vasculitis. *N. Engl. J. Med.* 337, 1512.

Jennette, J. C., Falk, R. J., Andrassy, K., Bacon, P. A., Churg, J., Gross, W. L., Hagen, E. C., Hoffman, G. S., Hunder, G. G., Kallenberg, C. G., *et al.* (1994). Nomenclature of systemic vasculitides. Proposal of an international consensus conference. *Arthritis Rheum.* 37(2), 187–192.

Kerr, G. (1995). Takayasu's arteritis. *Rheum. Dis. Clin. North Am.* 21, 1041.

Lee, E., Smith, H., Miller G. L., *et al.* (1984). Ischemic pseudomembranous colitis with perforations due to polyarteritis nodosa. *Am. J. Gastroenterol.* 79, 35.

Levine, S. M., and Hellmann, D. B. (2002). Giant cell arteritis. *Curr. Opin. Rheumatol.* 14, 3.

Lhote, F., and Guillevin, L. (1993). Polyarteritis nodosa, microscopic polyangiitis and Churg–Strauss syndrome. *Rheum. Dis. Clin. North Am.* 21, 911.

Lopez, L., Schocket, A., Standford, R., *et al.* (1980). Gastrointestinal involvement in leukocytoclastic vasculitis and polyarteritis nodosa. *J. Rheumatol.* 7, 677.

Rao, J. K., Weinberger, M., Oddone, E. Z., *et al.* (1995). The role of antineutrophilic cytoplasmic antibody (C-ANCA) testing in the diagnosis of Wegener granulomatosis: A literature review and meta-analysis. *Ann. Intern. Med.* 123, 925.


# Vasoactive Intestinal Peptide (VIP)


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**nitric oxide (NO)** Chemical that mediates smooth muscle relaxation through activation of guanylate cyclase and production of cyclic GMP; vasoactive intestinal peptide acts through the single-transmembrane natriuretic peptide clearance receptor C, coupled to $G_{i1}$ and $G_{i2}$ proteins, to activate endothelial nitric oxide synthase, with resultant production of NO.

**vasoactive intestinal peptide (VIP) family** VIP and peptides homologous to VIP, including secretin, glucagon, PHM (a 27-amino-acid peptide having N-terminal histidine and C-terminal methionine), pituitary adenylate cyclase-activating peptide (of either 27 or 38 amino acids in length), gastric inhibitory peptide, growth hormone-releasing factor, and helodermin.

**$VPAC_1$ and $VPAC_2$** Specific, high-affinity membrane receptors for vasoactive intestinal peptide; both are $G_s$-coupled receptors spanning the plasma membrane seven times.

**WDHA** A syndrome of watery diarrhea, hypokalemia, and achlorhydria, associated with neuroendocrine vasoactive intestinal peptide-secreting tumors (VIPoma); also known as pancreatic cholera or Verner-Morrison syndrome.

**In 1902, W. Bayliss and E. Starling described secretin and established the field of endocrinology. In their landmark communication to the Royal Society of London, they noted that "... secretin is associated with another body with a pronounced lowering effect on the blood pressure." This may be the first reference to vasoactive intestinal peptide (VIP), identified by S. Said and V. Mutt in 1970 as a polypeptide from the small intestine that induces systemic**

**vasodilation, hypotension, increased cardiac output, respiratory stimulation, and hyperglycemia. VIP is now known to have protean biological, physiological, and clinical effects; a Medline search yielded ~10,000 articles published with VIP as a keyword. This article will examine the peptide structure of VIP, its receptors, cellular action, distribution, biological effects, and clinical relevance.**

## VASOACTIVE INTESTINAL PEPTIDE: PEPTIDE STRUCTURE AND HOMOLOGOUS PEPTIDES

Vasoactive intestinal peptide (VIP) is composed of 28 amino acid residues and belongs to a family of homologous bioactive peptides that include PHM (27 amino-acid peptide having N-terminal histidine and C-terminal methionine), pituitary adenylate cyclase-activating peptide (PACAP; of either 27 or 38 amino acids in length), secretin, glucagon, gastric inhibitory peptide (GIP), growth hormone-releasing factor (GHRF), and helodermin (Gila monster venom) (Fig. 1). PACAP is a neuropeptide and secretin, glucagon, GIP, and GHRH are hormones. PHM is co-synthesized with VIP (see below).

Human, cow, pig, goat, dog, and rat (but not guinea pig) VIPs are identical, suggesting conservation during mammalian evolution. Nonmammalian VIP (chicken, alligator, frog, trout, bowfin, dogfish, cod, and goldfish) differs from the human peptide at only four or five positions.

Peptide modeling suggests that VIP exhibits a central α-helix from Val-3 to Asn-24 with random coiled N- and C-termini. Studies of VIP analogues and alanine substitutions suggest that His-1, Val-5, Thr-11, Arg-14, Lys-15, Lys-21, Asn-28, Leu-23, and Ile-26 interact directly with VIP receptors.

Human VIP is synthesized as a precursor protein (prepro-VIP) of 170 amino acids (MW 19,169) containing, in addition to VIP, a signal peptide of ~20 amino acids and PHM. As shown in Fig. 1, human PHM exhibits marked homology to VIP (in the rat, substitution of the N-terminal methionine by isoleucine yields PHI); its effect is mediated through VIP receptors. In humans, prepro-VIP mRNA is transcribed from an 8837 bp gene that encodes seven exons and six introns and that is located on chromosome 6q24.

| | | |
|---|---|---|
| **VIP** | HSDAVFTDNY TRLRKQMAVK KYLNSILN | |
| **PACAP** | HSDGIFTDSY SRYRKQMAVK KYLAAVLGKR YKQRVKNKN | [19] |
| **PHM** | HSDGVFTSDF SKLLGQLSAK KYLESLM | [13] |
| **Helodermin** | HSDAIFTQQY SKLLAKLALQ KYLASILGSS TSPPP | [14] |
| **Secretin** | HSDGTFTSEL SRLREGARLQ RLLQGLI | [10] |
| **GHRF** | YADAIFTSDY RKVLGQLSAR KLLQDIMSQR ... L (44) | [8] |
| **Glucagon** | HSQGTFTSDY SKYLDSRRAQ DVFQWLMNT | [6] |
| **GIP** | YAEGTFISDY SIAMDDIRQQ DPVNWLL | [4] |

FIGURE 1 VIP peptide family. The amino acid sequences of human VIP and of homologous peptides are shown. With VIP serving as reference, the identical amino acids are underlined and the number of identical amino acids for each peptide is given in brackets.

## VASOACTIVE INTESTINAL PEPTIDE RECEPTORS

This section will examine the receptors specific for VIP that mediate the different biologic effects of this peptide. Although VIP interacts with many receptors with variable degrees of affinity and specificity, only two receptors with high affinity for VIP are identified, named $VPAC_1$ and $VPAC_2$ in 1998. Of the peptides of the VIP family, PHM also acts through $VPAC_1$ and $VPAC_2$, since no receptor specific for PHM has been identified. PACAP also binds to $VPAC_1$ and $VPAC_2$; it also binds with high affinity to $PAC_1$, a receptor with low affinity for VIP.

### $VPAC_1$

Previously known as the VIP, $VIP_1$, VIP/PACAP type II receptor, or PVR2 receptor, $VPAC_1$ was extensively characterized functionally and biochemically in the 1980s. It was cloned in 1992 from the rat lung by Ishihara *et al.* and the human counterpart was identified in 1993–1994. The human $VPAC_1$ contains 460 amino acids with a predicted MW of 51,929 (including a signal sequence of 30 amino acids); it exhibits 81% amino acid sequence identity with its rat counterpart. Paralleling the homology of their ligands, there is marked homology between $VPAC_1$ and the receptors for PACAP ($PAC_1$), secretin, GHRF, glucagon, parathyroid hormone (PTH), glucagon-like peptide I, and calcitonin. The human chromosomal location of $VPAC_1$ is 3p22. There is no known splice variant of this receptor.

As illustrated in Fig. 2, hydropathy analysis predicts seven transmembrane domains, characteristic of G-protein-coupled receptors, and a large N-terminal extracellular domain of 114 amino acids (excluding the signal sequence). Studies of chimeric secretin–VIP receptors support a key role for this N-terminal domain in VIP recognition. Similar to other G-protein-coupled receptors, the second and third intracellular loops may interact with $G_s$, the G-protein coupled to $VPAC_1$, and the intracellular C-terminus may mediate receptor desensitization. There are four potential sites for N-glycosylation, one site for cyclic AMP (cAMP)-dependent phosphorylation, and three sites for protein kinase

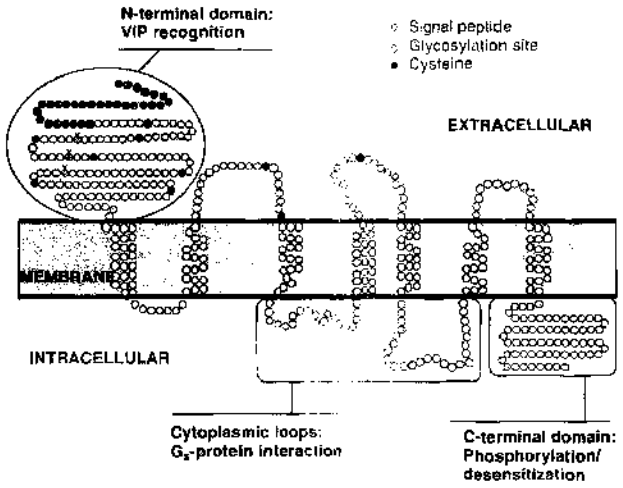


FIGURE 2 Predicted structure of $VPAC_1$. Each amino acid is represented as a circle and the amino acids of the signal peptide, cysteine residues, and potential glycosylation sites are indicated, respectively, by gray shading, black shading, and a Y symbol. The seven-transmembrane domains are characteristic of G-protein-coupled receptors. The large extracellular N-terminus is the domain for VIP recognition; the second and third cytoplasmic loops and the cytoplasmic C-terminal domain contain sites for $G_s$-protein interaction and phosphorylation/desensitization. Modified from Gaudin *et al.* (1995). *Biochem. Biophys. Res. Commun.* 211, 901–908.

C phosphorylation. Of the 10 extracellular cysteines, the residues at positions 50, 64, 72, 86, 105, and 122 in the N-terminal domain are crucial for VIP binding. The Asp-3 of VIP penetrates into the transmembrane region of the receptor, in close proximity to the conserved Arg-188 and Lys-195 on the second transmembrane domain.

Functional studies of $VPAC_1$ demonstrate a VIP-binding affinity of 0.6 nM and the following order of potency: VIP = PACAP-27 > PACAP-38 > helodermin > GHRF = PHM > secretin. Selective $VPAC_1$ receptor agonists include the VIP/GRF hybrid [Lys-15, Arg-16, Leu-27]VIP(1–7)GRF(8–27)-$NH_2$, chicken [Arg-16]-secretin (which also activates the secretin receptor), and [Ala-11, -22, -28]VIP (>1000-fold discrimination between $VPAC_1$ and $VPAC_2$). [Acetyl-His-1, D-Phe-2, Lys-15, Arg-16]VIP(3–7)GRF(8–27)-$NH_2$ and (N-stearyl, norleucine-17)VIP hybrid are reported antagonists of $VPAC_1$.

Using Northern blotting, $VPAC_1$ is localized to lung > prostate > peripheral leukocyte, liver, brain, small intestine > colon, heart, spleen > placenta, kidney, thymus, testis (decreasing order of expression). By receptor autoradiography $VPAC_1$ is expressed in many epithelial cells, such as hepatocytes, mucosal cells of the stomach and colon acinar and/or duct cells of the breast, pancreas, and lung, and glandular cells of the thyroid, prostate, uterus, and adrenal medulla.

### $VPAC_2$

$VPAC_2$, also known as the helodermin-preferring VIP receptor, $VIP_2$, PACAPR-3, or PVR3 receptor, was first cloned from the rat olfactory bulb and its human counterpart was subsequently identified. Its human chromosomal location is 7q36.3. Human $VPAC_2$ contains 438 amino acids (including a putative 23-amino-acid signal sequence) and exhibits an 86% amino acid identity with the rat $VPAC_2$. Homology with other receptors was much lower: 49% amino acid identity with human $VPAC_1$ and 52% identity with $PAC_1$. Similar to $VPAC_1$, the predicted structure of $VPAC_2$ includes seven transmembrane domains and a large extracellular N-terminal domain. There are 10 extracellular cysteines, conserved from $VPAC_1$, and three potential sites for N-glycosylation.

Binding and functional studies of $VPAC_2$ show the following order of potency: PACAP-38 ≥ helodermin ≥ VIP = PACAP-27. Unlike $VPAC_1$, $VPAC_2$ does not bind secretin, even at 1 μM. Ro 25-1553 is a highly selective agonist for $VPAC_2$ and may be used for bronchodilation.

By receptor radioautography, $VPAC_2$ is found on smooth muscle cells (e.g., stomach, blood vessels) and on thymic lymphoid cells.

### Related Receptors

A protein has been identified from the human jejunum exhibiting 100% homology with the 428 C-terminal amino acids of $VPAC_1$ but completely divergent at the N-terminal 67 amino acids. This protein does not bind VIP and its functional significance remains to be determined.

As discussed below, VIP may also interact with the single-transmembrane natriuretic peptide clearance receptor, coupled with $G_{i1}$ or $G_{i2}$, to stimulate endothelial nitric oxide synthase (eNOS) in smooth muscle cells.

## DISTRIBUTION AND METABOLISM

### Distribution

VIP is widely distributed in the human body, primarily within the neurons of the central and peripheral nervous systems. Over the length of the gastrointestinal (GI) tract, it is present in large amounts in both its mucosal and muscular layers, with a trend toward more abundant peptide and higher mucosal/muscular

peptide ratio in the distal portions of this tract (with focal increases in the proximal duodenum and right colon). VIP is also present in the gallbladder and is abundant around sphincters (e.g., lower esophageal sphincter, pylorus, and sphincter of Oddi).

Within the gut wall, VIP is found in ~2.5% of the neurons of the myenteric, or Auerbach's, plexus and in ~45% of the neurons of the submucous, or Meissner's, plexus. As shown in Fig. 3, VIP-containing neurons in the myenteric ganglia project distally to other myenteric and submucous ganglia, to underlying circular muscles, and to prevertebral ganglia, suggesting a role for VIP in mediating the descending inhibition of a peristaltic wave. VIP-containing neurons in the submucous ganglia project to submucous arterioles and to the mucosa, suggesting additional functions for this peptide in regulating mucosal transport and local blood flow.

In the exocrine GI system, VIP is also present in the postganglionic cholinergic neurons that innervate glandular tissues such as submandibular salivary glands and pancreas. In these glands, the presence of VIP-containing nerve endings around small blood vessels, acini, and ducts again suggests a vasoregulatory and secretory function for VIP.

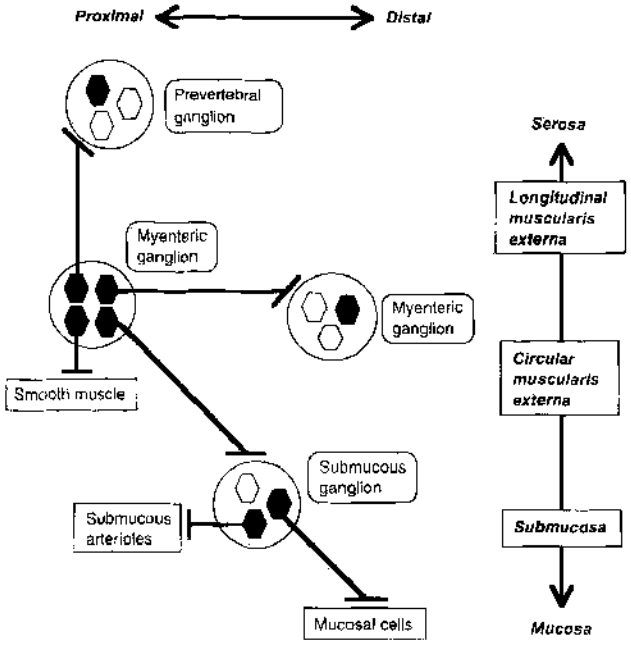


FIGURE 3 Organization of VIP-containing neurons in the GI tract. VIP-containing neurons (shown in black) in the myenteric and submucous ganglia of the GI tract and their projections to other ganglia and target cells (smooth muscles of the bowel wall, submucous arterioles, and secretory mucosal cells) are depicted. For orientation, the proximal (oral) and distal (anal) directions are shown at the top and the different layers of the bowel wall are shown on the right.

### Vasoactive Intestinal Peptide Release and Metabolism

As a neurotransmitter, VIP is released from nerve endings (e.g., following neuronal depolarization) to act on adjacent cells. Locally, this VIP is cleared through internalization of the VIP–receptor complexes by the target cell, followed by intracellular degradation. Cell surface peptidases may also inactivate VIP, as reported for gastric smooth muscle membranes.

VIP may also evade local degradation to enter the vascular compartment. Indeed, VIP plasma concentrations (systemic basal levels: ~20–50 pg/ml; portal basal levels: 40–100 pg/ml) may increase following stimulation of VIP release (e.g., with oral lipids or intravenous calcium, oxytocin, or neostigmine). The entire GI tract is the main source for circulating VIP. VIP is rapidly cleared from the circulation, with a plasma half-life as short as 1–3 min. The major contribution of hepatic clearance in this process is suggested by the higher levels of VIP in the portal (versus systemic) circulation, elevated peptide levels in patients with hepatic failure, and hepatic extraction of labeled VIP injected into the portal circulation. In the systemic circulation, VIP is extracted by the lung.

## BIOLOGIC EFFECTS OF VIP

Because VIP and its receptors are widely distributed in the GI tract, it has extensive effects on the digestive system. For over two decades, it has been established that VIP stimulates secretion from epithelial cells and relaxes smooth muscles; recently, it has also been recognized that VIP modulates inflammation and cellular growth and differentiation. The cellular mechanisms for these actions are illustrated in Fig. 4.

### Stimulation of Secretion

The secretory effect of VIP has been established *in vitro* and *in vivo*, with cultured cells, animal models, and human subjects. VIP stimulates the secretion of fluid and electrolytes from the gallbladder, small intestine, and colon, of EGF and bicarbonate from duodenal Brunner's glands, and of bicarbonate and digestive enzymes from the exocrine pancreas. In promoting this secretory effect, VIP may act alone or in concert with other agents (e.g., VIP potentiates the secretory effect of cholecystokinin on pancreatic acini).

The mechanism underlying VIP-stimulated secretion has been elucidated with T84 colonocytes and is

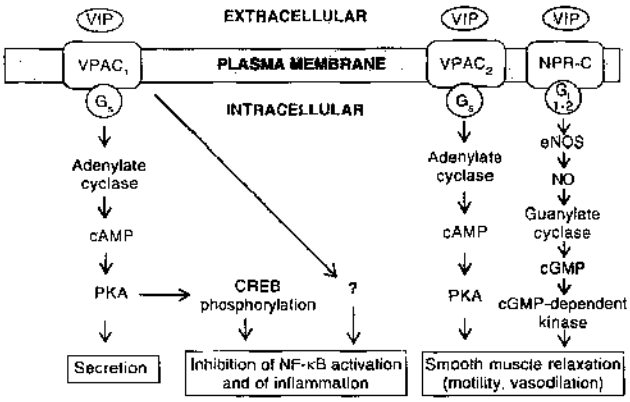


FIGURE 4 Biologic actions of VIP. The cellular mechanisms underlying the biologic effects of VIP on secretion, inflammation, and smooth muscle relaxation are depicted. $VPAC_1$ and $VPAC_2$, high-affinity VIP receptors; NPR-C, natriuretic peptide clearance receptor; $G_s$, $G_{i1}$, and $G_{i2}$, G-protein subtypes mediating the effect of VIP; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; PKA, cAMP-dependent protein kinase A; CREB, cAMP regulatory element-binding protein. Modified from Murthy *et al.* (1998). *Am. J. Physiol.* 275, C1409–C1416.

illustrative of VIP-induced secretion in other tissues. VIP interacts with $VPAC_1$, located on the basolateral membrane of these cells, to activate adenylate cyclase through $G_s$. The subsequent increase in intracellular cAMP will activate cAMP-dependent protein kinase (PKA), promote phosphorylation and activation of the relevant ion transport pathways (e.g., basolateral cAMP-dependent $K^+$ channel and apical cystic fibrosis transmembrane conductance regulator $Cl^-$ channel), and induce the secretion of electrolytes (primarily $Cl^-$) and fluid. Agents acting via other signaling pathways may potentiate this response, either through cross talk between the transduction mechanisms or through activation of additional ion transport pathways (e.g., $Ca^{2+}$-activated $K^+$ channels).

## Smooth Muscle Relaxation

In tissue and animal models, VIP induces the relaxation of smooth muscles from the stomach, small and large intestine, GI sphincters, gallbladder, and blood vessels. This effect is mediated through two pathways. By activating the $G_s$-coupled $VPAC_2$, VIP activates adenylate cyclase to promote intracellular cAMP production, stimulate PKA, and activate the proteins mediating smooth muscle relaxation. In addition, VIP may interact with the natriuretic peptide clearance receptor, coupled to $G_{i1}$ and $G_{i2}$, to promote $Ca^{2+}$ influx and $[Ca^{2+}]_i$ increase. The subsequent activation of the $Ca^{2+}$/calmodulin-dependent eNOS leads to the generation of nitric oxide (NO), NO-dependent activation of soluble guanylate cyclase, generation of cGMP, activation of cGMP-dependent kinase, and relaxation of smooth muscle cells.

In the gastric fundus, NOS and VIP are co-localized in the majority of myenteric neurons and NO also stimulates the release of VIP from nerve endings, further enhancing the interaction between VIP and NO. Conversely, VIP may also stimulate myenteric neurons to release substances that induce smooth muscle contraction (e.g., in guinea pig ileum).

## Modulation of Inflammation

VIP suppresses the production of many pro-inflammatory agents by monocytes and macrophages. This effect, mediated through $VPAC_1$, occurs via inhibition of the transactivation of nuclear factor κB (NF-κB), a pleiotropic transcription factor that regulates the production of many pro-inflammatory agents [e.g., tumor necrosis factor α, interleukin-12 (IL-12), IL-1, IL-6, NO] and chemokines (e.g., IL-8, RANTES, monocyte chemoattractant protein-1, intracellular adhesion molecule-1). In unstimulated cells, NF-κB is present in the cytosol as a p50/p65 heterodimer, bound to the inhibitor IκB. On stimulation, IκB is phosphorylated and degraded, allowing NF-κB to translocate to the nucleus. In the nucleus, NF-κB promotes the transcription of inflammatory agents by binding to the corresponding DNA, in concert with other transcription factors, such as the CREB-binding protein (CBP, where CREB is cAMP regulatory element-binding protein) and TATA-box-binding protein (TBP).

VIP inhibits NF-κB transactivation at three levels. First, through a cAMP-independent pathway, VIP inhibits NF-κB nuclear translocation and subsequent DNA binding. Second, it induces the phosphorylation of CREB, allowing it to compete against p65 for CBP binding. Third, it inhibits the phosphorylation of TBP and its binding to p65 and the TATA-box. The effects of VIP on CBP and TBP are both mediated through cAMP. The significance of these actions on GI inflammation awaits further studies.

## Effects on Cellular Growth and Differentiation

VIP also appears to modulate apoptosis and the growth and differentiation of neuronal and immune cells. It may also promote the proliferation of many neoplastic cells; $VPAC_1$ receptor antagonists have been used *in vitro* to inhibit tumor growth.

## CLINICAL ASPECTS

### Vasoactive Intestinal Peptide-Secreting Tumors (VIPoma)

In 1958, Verner and Morrison first described a syndrome of profuse, refractory, and watery diarrhea, hypokalemia, and achlorhydria in association with non-β islet cell pancreatic tumors. Known variously as pancreatic cholera, WDHA (for watery diarrhea, hypokalemia, and achlorhydria), and the VIPoma or Verner-Morrison syndrome, this entity is associated with elevated levels of VIP in the serum or corresponding tumor.

Pancreatic cholera is the third most common manifestation of pancreatic neuroendocrine tumors, after hypoglycemia from insulinomas and peptic symptoms from gastrinomas. VIPomas account for 2–7% of GI neuroendocrine tumors and occur with an annual incidence of 1 in $10^7$ (mean patient age: 49 years; female/male preponderance: 3/1). Ninety percent of these tumors are encountered in the pancreas, where they usually occur as solitary tumors in the body or tail (75% of pancreatic cases). Nonpancreatic VIPomas occur mostly along the autonomic nervous system and in the adrenal medulla. Similar to other GI neuroendocrine tumors, approximately 60% of VIPomas are malignant. Most VIPomas also synthesize one or more additional neuropeptides (e.g., 39% of VIPomas secrete pancreatic polypeptide).

Whereas the liver and lung normally clear circulating VIP, excessive VIP secreted by tumors reaches distal organs to affect their function. Pancreatic cholera, occurring in half of the patients with VIPoma, is caused by the stimulation of secretion from intestinal crypt cells, manifested clinically as a watery, secretory, and fasting diarrhea associated with hypokalemia from fecal $K^+$ losses of up to 400 mEq/day. By inhibiting gastric secretion, VIPomas also cause achlorhydria or, more commonly, hypochlorhydria. Cross-reactivity between VIP and the hepatic glucagon receptor may account for the glucose intolerance and the hyperglycemia observed, respectively, in 50 and 18% of affected patients, whereas cross-reactivity with the PTH receptor may induce hypercalcemia in 25–75% of patients. Vasodilation promoted by VIP may cause an initial flushing and rash on the head and upper trunk in 20% of VIPoma patients; desensitization may subsequently reduce these symptoms.

Even though the VIPoma syndrome is a well-established entity, because of its rarity, it is still recognized only after an average duration of symptoms of 3 years. This diagnosis should be entertained for cases of secretory diarrhea productive of liters of isotonic watery stools that persist after 2–3 days of fasting. The diagnosis is supported by a fasting plasma VIP > 200 pg/ml.

VIPomas can be localized by conventional and endoscopic ultrasound, computed tomography scanning, angiography, and magnetic resonance. Because all neuroendocrine tumors (except insulinomas) express high-affinity somatostatin receptors, nuclear scanning with labeled octreotide, a stable somatostatin analogue, can effectively detect these tumors. Indeed, the experience with gastrinomas, representative of pancreatic neuroendocrine tumors, suggests that octreotide scanning is the single most sensitive method for imaging VIPomas, equal to all other imaging modalities combined (respective sensitivities of 58 and 70% for primary and metastatic tumors).

The most effective medical treatment for diarrhea is octreotide (100–150 μg subcutaneous every 8 h), which acts both on tumor cells to inhibit the synthesis and release of VIP and on intestinal crypt cells to inhibit secretion. Because of this dual effect, reduction of diarrhea (rather than normalization of VIP levels) may be a reasonable end-point. Adverse effects from octreotide include pain at the site of injection, imbalance of glucose metabolism, pancreatic exocrine insufficiency with steatorrhea, inhibition of gallbladder contraction, and gallstone formation.

Other agents advocated for the treatment of this syndrome include $\alpha_2$-adrenergic agonists (e.g., clonidine and lidamidine), trifluoperazine, indomethacin, lithium, and metoclopramide. In addition, streptozotocin is a useful chemotherapeutic agent. An immunoglobulin G against VIP, which hydrolyzes VIP *in vitro*, may also have therapeutic potential.

For benign VIPomas, surgery after tumor localization will be curative. For malignant tumors, surgical debulking alone may be helpful in 40% of cases.

### VIP Scanning

VIP receptors are present not only in many tissue types, but also on tumors derived from these tissues. $VPAC_1$ receptors are expressed by carcinomas of the breast, prostate, pancreas, lung, colon, stomach, liver, and bladder, as well as by lymphomas and meningiomas, whereas $VPAC_2$ receptors are expressed by leiomyomas. VIP receptors can therefore be used to detect these tumors. Indeed, in patients with various GI cancers (colorectal, pancreatic, gastric, carcinoid tumors, and insulinomas), most primary lesions and associated metastases are detected by scintigraphy with $^{123}$I-VIP. The high quality of the positive scans reflects the abundance of VIP receptors on these tumors relative to normal tissue and blood cells, except for the lung

where background VIP uptake is high. The false-negative scans are probably caused by the absence of VIP receptors or their blockade by endogenous ligands. Transient hypotension is the only side effect observed with VIP scanning. Development of $^{99}$Tc-labeled VIP may further enhance this scanning technique.

### Vasoactive Intestinal Peptide in Cirrhosis

Because VIP is extracted by the liver and induces vasodilation, it has been postulated that, in cirrhosis, hepatic clearance of VIP is impaired, allowing VIP to produce some of the circulatory disturbances associated with this condition. In animal models and patients with cirrhosis, significant, but modest, increases in plasma VIP concentrations are observed. However, the circulatory effects of these increased VIP levels may be minimized by a blunted cardiovascular response. Indeed, although VIP infusion increased the portal tributary blood flow in normal rats, it did not affect any hemodynamic parameter in rats with cirrhosis caused by bile duct ligation.

## SUMMARY AND CONCLUSION

Following its discovery in 1970, it was soon recognized that VIP stimulates epithelial cell secretion as well as smooth muscle cell relaxation and that VIP-producing tumors can cause a syndrome of watery diarrhea, hypokalemia, and achlorhydria. Additional roles for VIP in modulating inflammation, immune response, and cellular growth and differentiation are also being clarified. Furthermore, scintigraphy with radiolabeled VIP is being developed as a tool to detect GI tumors and clarifying the structure of VIP receptors and understanding their interaction with VIP will facilitate the design of beneficial agonists and antagonists. The relevance of VIP to GI physiology and pathophysiology is therefore continually expanding.

### Acknowledgments

This work was partially supported by National Institutes of Health Grant RO1 DK 35885, VA Merit Review funding, and Cystic Fibrosis Foundation RDP R565. The author is indebted to Eric Nguyen for gathering source materials and Dr. Gabriel Makhlouf for clarifying the effects of VIP on smooth muscle cells.

### See Also the Following Articles

**Glucose-Dependent Insulinotropic Polypeptide (GIP) • Growth Hormone • Nitric Oxide • Pituitary Adenylate Cyclase Activating Peptide (PACAP) • Secretin • Vipoma**

### Further Reading

Bloom, S. R., Polack, J. M., and Pearse, A. G. E. (1973). Vasoactive intestinal peptide and watery diarrhea syndrome. *Lancet* II, 14–16.

Costa, M., and Furness, J. B. (1983). The origins, pathways and terminations of neurons with VIP-like immunoreactivity in the guinea-pig small intestine. *Neuroscience* 8, 665–676.

Couvineau, A., Rouyer-Fessard, C., Darmoul, D., Maoret, J. J., Carrero, I., Ogier-Denis, E., and Laburthe, M. (1994). Human intestinal VIP receptor: Cloning and functional expression of two cDNA encoding proteins with different N-terminal domains. *Biochem. Biophys. Res. Commun.* 200, 769–776.

Delgado, M., and Ganea, D. (2001). Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide inhibit nuclear factor-κB-dependent monocytic cell line THP-1. *J. Biol. Chem.* 276, 369–380.

Harmar, A. J., Arimura, A., Gozes, I., Journot, L., Laburthe, M., Pisegna, J. R., Rawlings, S. R., Robberecht, P., Said, S. I., Sreedharan, S. P., and Washek, J. A. (1998). International Union of Pharmacology. XVIII. Nomenclature of receptors for vasoactive intestinal peptide and pituitary adenylate cyclase activating polypeptide. *Pharmacol. Rev.* 50, 265–270.

Itoh, N., Obata, K., Yanaihara, N., and Okamoto, H. (1983). Human preprovasoactive intestinal polypeptide contains a novel PHI-27-like peptide, PHM-27. *Nature* 304, 547–549.

Lee, S. I., Huang, M., Ma, Z., and Rorstad, O. (1996). Vasoactive intestinal peptide in cirrhotic rats: Hemodynamic effects and mesenteric arterial receptor characteristics. *Hepatology* 23, 1174–1180.

Murthy, K. S., Teng, B.-Q., Jin, J.-G., and Makhlouf, G. M. (1998). G protein-dependent activation of smooth muscle eNOS via natriuretic peptide clearance receptor. *Am. J. Physiol.* 275, C1409–C1416.

Park, S. K., O'Dorisio, M. S., and O'Dorisio, T. M. (1990). Vasoactive intestinal polypeptide-secreting tumours: Biology and therapy. *Bailliere Clin. Gastroenterol* 10, 673–696.

Said, S. I., and Mutt, V. (1970). Polypeptide with broad biological activity: Isolation from small intestine. *Science* 168, 1217–1218.

Sreedharan, S. P., Huang, J.-X., Cheung, M.-C., and Goetzl, E. J. (1995). Structure, expression, and chromosomal localization of type I human vasoactive intestinal peptide receptor gene. *Proc. Natl. Acad. Sci. USA* 92, 2939–2943.

Svoboda, M., Tastenoy, M., Van Rampelbergh, J., Goossens, J.-F., De Neef, P., Waelbroeck, M., and Robberecht, P. (1994). Molecular cloning and functional characterization of a human VIP receptor from SUP-T1 lymphoblasts. *Biochem. Biophys. Res. Commun.* 205, 1617–1624.

Verner, J. V., and Morrison, A. B. (1974). Endocrine pancreatic islet disease with diarrhea. *Arch. Intern. Med.* 133, 492–500.

Verner, J. V. J., and Morrison, A. B. (1958). Islet cell tumor and a syndrome of refractory watery diarrhea and hypokalemia. *Am. J. Med.* 25, 374–380.

Virgolini, I., Raderer, M., Kurtaran, A., Angelberger, P., Banya, S., Yang, Q., Li, S., Banyai, M., Pidlich, J., Niederle, B., Scheithauer, W., and Valent, P. (1994). Vasoactive intestinal peptide-receptor imaging for the localization of intestinal adenocarcinomas and endocrine tumors. *N. Engl. J. Med.* 331, 1116–1121.

# Vipoma

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**multiple endocrine neoplasia type 1** An autosomal dominantly inherited disorder associated with endocrine tumors of the parathyroid, pituitary, and endocrine pancreas, as well as in some patients with tumors of other endocrine glands and skin manifestations.

**non-beta islet cell tumors** Pancreatic endocrine tumors arising from cells other than the insulin-producing beta cells of the islets of Langerhans.

**vipoma** An endocrine tumor, usually of the pancreas, that produces vasoactive intestinal peptide.

**Vipomas are rare tumors, with an annual incidence of 1 per 2 million or less. They are derived from neuroendocrine cells that produce and secrete vasoactive intestinal polypeptide (VIP). Most (80–90%) vipomas arise in the pancreas, are large (several centimeters), and are solitary. Rarely, they may arise from intestinal neuroendocrine tumors, bronchial carcinomas, pheochromocytomas, ganglioneuromas, or ganglioneuroblastomas. A small percentage of vipomas are associated with multiple endocrine neoplasia type 1 (MEN-1) syndrome, with prior, coexistent, or subsequent development of hyperparathyroidism, pituitary tumors, adrenal tumors, and/or thyroid tumors.** The majority of vipomas are malignant.

Unlike most pancreatic tumors, vipomas do not usually cause symptoms despite their location in the pancreas. Thus, symptoms associated with other pancreatic tumors, such as pain in the epigastrium or back, nausea, vomiting, and jaundice, are conspicuously absent in these patients. Instead, symptoms in patients with vipomas derive from the actions of excessive amounts of VIP released into the portal circulation and ultimately into the systemic circulation.

## PHYSIOLOGY

Vasoactive intestinal peptide (VIP) is a polypeptide with structural homologies to other peptides such as glucagon and secretin. Though originally described as a vasoactive intestinal-derived peptide that inhibits gastric acid secretion, VIP under physiologic conditions is produced mainly by enteric or central nervous system neurons and thus is a neuropeptide. The physiologic effects of VIP acting as a neuropeptide in the gut and the brain are not completely understood, although current evidence suggests that VIP acts in the gut as an inhibitory neurotransmitter that induces smooth muscle relaxation. For example, VIP in postganglionic esophageal neurons has been proposed to be the noncholinergic, nonadrenergic neurotransmitter that relaxes the lower esophageal sphincter, although nitric oxide has also been suggested to play this role. VIP is also a potent vasodilator.

## CLINICAL FEATURES

Non-beta islet cell tumors of the pancreas may produce large amounts of peptides normally produced in the pancreas, such as glucagon and somatostatin, or peptides not normally produced in the pancreatic islets, such as gastrin or VIP. Vipomas are also called Verner-Morrison syndrome or the watery diarrhea hypokalemia hypochlorhydria syndrome, the latter of which describes some of the cardinal features of the disease. VIP, like cholera toxin and the heat-labile toxin of *Escherichia coli*, activates adenylate cyclase and increases concentrations of cyclic AMP within intestinal epithelial cells, and this increase has the effect of blocking NaCl absorption by these enterocytes. In addition, high concentrations of VIP, like the above-mentioned bacterial toxins, can stimulate intestinal chloride secretion. The consequence of reduced salt absorption and chloride secretion by the gut is a watery (nonbloody) diarrhea that contains large amounts of potassium and bicarbonate. The diarrhea in patients with vipomas can be prodigious and lead to life-threatening volume dehydration, hypotension or shock, hypokalemia, hyperchloremic metabolic acidosis, and hyponatremia. In fact, vipoma is sometimes referred to as pancreatic cholera syndrome because of its similarities to cholera. Classically, diarrhea in vipoma patients continues even when the patient fasts, although feeding can exacerbate the diarrhea due to the additional fluid and electrolytes entering the gut with a meal. Other symptoms (besides diarrhea) manifested by some patients with vipoma include weight loss, abdominal cramps, and flushing; the last symptom is a consequence of the vasoactive properties of VIP. Although high circulating levels of VIP also reduce gastric acid secretion in many of these patients, this

 

typically has no clinical consequences. Hypercalcemia and/or hyperglycemia may also be present in up to half of patients with vipomas.

## DIAGNOSIS

Diagnosis of vipomas is difficult due to the rarity of the syndrome and many diseases that can produce chronic diarrhea. Furthermore, radioimmunoassay measurement of plasma VIP levels is performed only in certain specialized laboratories. One suggested approach is to measure the plasma VIP level in a reference laboratory only after an exhaustive search for other, more common causes of chronic diarrhea has been made (e.g., celiac sprue, Crohn's disease, laxative abuse). If plasma VIP is elevated (>190 pg/ml in most laboratories), a search for a tumor should be initiated since the test is highly specific. Assay sensitivity is fairly high (close to 90%), so repeating the test for VIP levels, if normal, has a finite but low utility. Probably the most useful test for localizing the tumor is endoscopic ultrasonography, but this test is invasive and expensive and requires considerable technical expertise. Radioactive scintigraphy using labeled octreotide is more widely available and is noninvasive. Abdominal computed tomography (CT) scan is also a good initial test because it is noninvasive and widely available. Most vipomas are large and therefore are evident on CT scan.

## STAGING AND THERAPY

Once the diagnosis of vipoma has been established, the extent of the tumor should be addressed. If there is evidence of spread to the liver, which occurs at the time of diagnosis in approximately 40–80% of cases, palliative therapy of the patient's symptoms caused by the tumor is indicated. Palliative therapy to control symptoms primarily consists of long-acting somatostatin analogues that effectively control the diarrhea in most patients. Glucocorticoids may be effective if the patient fails to respond to a somatostatin analogue. There is some evidence that chemotherapy with a variety of agents including streptozotocin, adriamycin, 5-fluorouracil, interferon-α, and etoposide may benefit a few patients. Furthermore, liver transplantation has been utilized to treat metastatic disease to the liver refractory to systemic chemotherapy.

If there is no evidence of spread of the tumor beyond the pancreas on CT scan and/or endoscopic ultrasonography, or only to local lymph nodes within the projected resection specimen, the patient should be referred to an experienced pancreatic or gastrointestinal surgeon for an attempt at cure. Cure of vipoma is possible in approximately one-third of patients referred for surgery.

### See Also the Following Articles

Multiple Endocrine Neoplasia (MEN) • Pancreatic Tumors, Other • Vasoactive Intestinal Peptide (VIP)

### Further Reading

Cellier, C., Yaghi, C., Cuillerier, E., *et al.* (2000). Metastatic jejunal VIPoma: Beneficial effect of combination therapy with interferon-α and 5-fluorouracil. *Am. J. Gastroenterol.* 95, 289–293.

Hengst, K., Nashan, B., Avenhaus, W., *et al.* (1998). Metastatic pancreatic VIPoma: Deteriorating clinical course and successful treatment by liver transplantation. *Z. Gastroenterol.* 36, 239–245.

Jensen, R. T., and Norton, J. A. (2002). Pancreatic endocrine tumors. *In* "Gastrointestinal and Liver Disease" (M. Feldman, L. S. Friedman, and M. H. Sleisenger, eds.), 7th Ed., pp. 988–1016. W. B. Saunders, Philadelphia, PA.

Masel, S. L., Brennan, B. A., Turner, J. H., *et al.* (2000). Pancreatic vasoactive intestinal polypeptide-oma as a cause of secretory diarrhea. *J. Gastroenterol. Hepatol.* 15, 457–460.

Yeh, C. N., Chen, M. F., and Chen, T. C. (2001). Surgical treatment of pancreatic vasoactive intestinal polypeptide-secreting tumor: A case report. *Hepatogastroenterology* 48, 421–423.

# Virtual Colonoscopy

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**adenomatous polyp** Histologic type of colon polyp that has an increased risk of becoming malignant; may not be associated with symptoms, but may cause bleeding leading to anemia.

**computer-aided detection** Use of software to assess and locate areas of concern in scanned images, alerting a radiologist to evaluate an area that may represent a potential lesion. Computers could be trained to analyze images and mark areas of concern, acting as a second observer.

**multidetector CT scanner** Newest technological advance in computer tomography scanners, with multiple (4, 8, 16, or 32) detector rows, allowing flexibility in slice thickness and faster scanning ability. Thinner slices increase diagnostic ability and may be used as the source data for a broad range of three-dimensional applications.

**Virtual colonoscopy, or computer tomography colonography, is an imaging technique that combines volumetrically acquired helical computer tomography scan data with advanced graphical software to create two- and three-dimensional views of the colon. This minimally invasive technique is a potential new tool for colorectal cancer screening and, compared to conventional colonoscopy, it may be more easily tolerated by patients.**

## INTRODUCTION

The majority of colorectal cancers arise from precursor adenomatous polyps. Detection and removal of these polyps while they are still benign can decrease the incidence of colorectal cancer. Current tools used for colorectal cancer screening include the fecal occult blood test (FOBT), flexible sigmoidoscopy, air contrast barium enema, and colonoscopy. Fecal occult blood testing is widely available and is the least expensive test but has been found to prevent the fewest cancers because of suboptimal accuracy. Colonoscopy is very sensitive for detecting polyps and cancers, but is the most invasive and expensive. Computed tomography (CT) colonography promises to change the way that colorectal cancer screening is performed. Performance studies have found that virtual colonoscopy has similar sensitivity to conventional colonoscopy for the detection of clinically significant polyps (those measuring 10 mm or larger).

## CT TECHNIQUE

Bowel cleansing is performed prior to the CT study because colonic segments containing residual stool or fluid will be poorly evaluated. Patients are required to ingest either an electrolyte lavage solution or saline cathartic starting the day before the CT scan. Oral intake is also limited to clear liquids or a low-residue diet on the day before the procedure. Colonic distension is obtained by placement of a small rectal tube and retrograde instillation of air or carbon dioxide. Compared to air, carbon dioxide is resorbed more rapidly through the colonic wall and may therefore be more comfortable for patients. The use of intravenous glucagon as an antispasmodic agent is controversial and is no longer employed by some investigators, who have not found a clear benefit.

Patients are scanned in two positions, typically supine and prone. Segments of the colon that are poorly evaluated in one position due to inadequate distension or residual material may be viewed in the opposing position, which often improves distension or uncovers areas due to shifting of residual material. Multidetector CT scanners can scan the entire colon is less than 20 seconds in each position. Low-dose radiation CT protocols are used with thin slice thickness. The acquired CT data are then transferred to a computer workstation, where the radiologist interprets the study. Two- and three-dimensional views are used in an integrated approach to detect polyps and cancer (Fig. 1). The three-dimensional images of the inside of the colon may be viewed as a movie loop and have an appearance similar to what is seen on an actual colonoscopy. Most radiologists use enlarged axial images for primary interpretation and will correlate with the three-dimensional endoluminal views only for problem solving, which has been found to decrease interpretation times from 40 minutes down to about 15 minutes. Areas of the colon with poor cleansing or suboptimal distension will limit the diagnostic ability of the CT (Fig. 2).

 

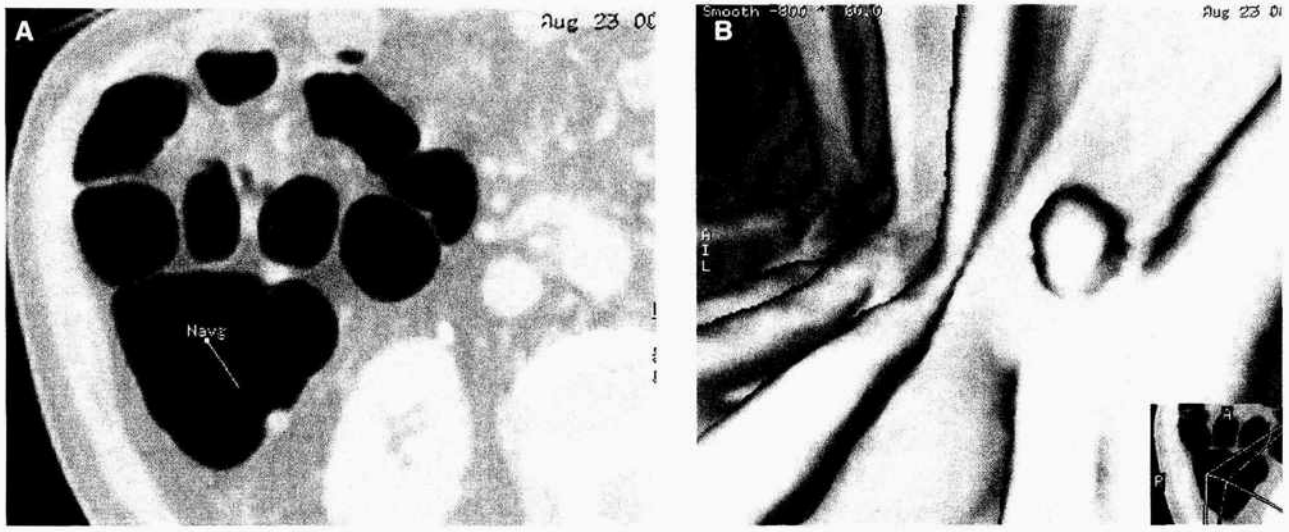


FIGURE 1 (A) Enlarged axial view of the ascending colon, showing a polyp located along the posterior wall. (B) Three dimensional endoluminal view demonstrates the appearance of the same ascending colon polyp.

## PERFORMANCE DATA

Current studies to date have found that CT colonography has a sensitivity range of 83–100% and a specificity range of 93–100% for the detection of polyps 10 mm or larger when using a per patient matching scheme. When each polyp found on virtual colonoscopy is matched with each polyp found on colonoscopy, the per polyp sensitivity range is 75–100% for the detection of polyps 10 mm or larger. CT colonography has been found to have low sensitivity for small polyps (less than 5 mm) and for flat lesions. The majority of published studies have been performed using single-detector CT scanners and in high-risk or symptomatic patients. Confirmatory performance studies need to be performed using multidetector CT scanners and in asymptomatic or screening patients.

CT colonography can evaluate the proximal colon when fiber-optic colonoscopy is unsuccessful due to a distal obstructing lesion or colonic tortuosity. CT colonography is an excellent alternative test in patients who have contraindications for conventional colonoscopy.

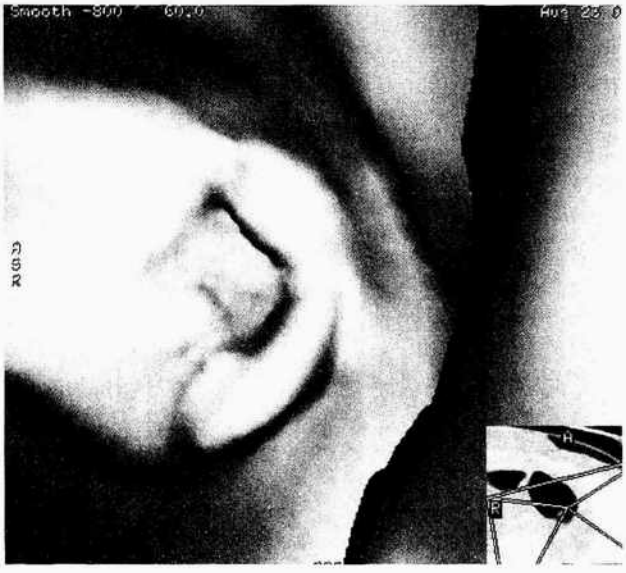

FIGURE 2 Appearance of an area of collapse on the three-dimensional endoluminal view. This imagery may simulate a carcinoma and must be correlated with the two-dimensional images.

## ADVANTAGES OF CT COLONOGRAPHY

Colonoscopy has traditionally been considered the "gold standard" for evaluation of the colon. CT colonography is also a total colon examination technique (Fig. 3) and offers several advantages compared with traditional colonoscopy. CT colonography is a less invasive examination compared with colonoscopy and there is no need for intravenous sedation. The total procedure time for CT colonography is very short, taking less than 10 minutes for setup and complete scanning in two positions. In addition to being able to examine portions of the colon not seen when colonoscopy is unsuccessful, CT colonography can more accurately localize a lesion to a particular segment. CT colonography also has the ability to detect pathology

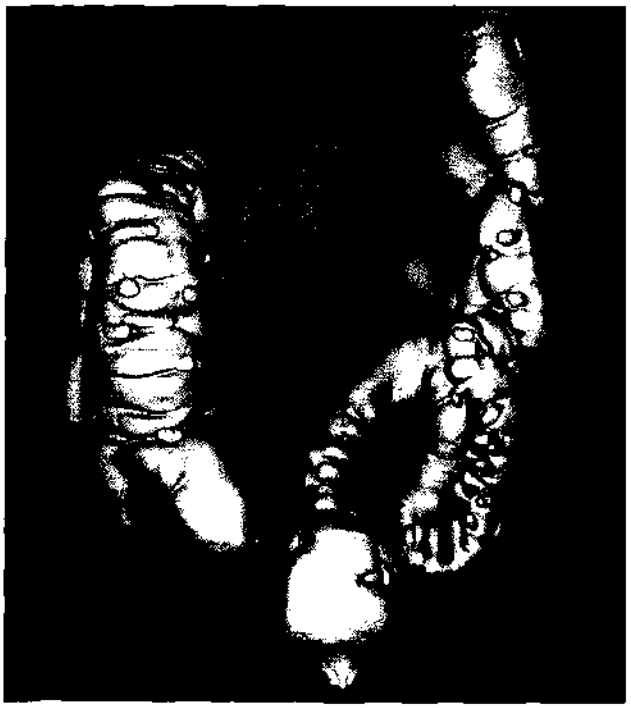

FIGURE 3 Three-dimensional external view of the entire colon in a patient with diffuse diverticulosis.

outside of the colon and can screen the remainder of the abdomen and pelvis without additional radiation.

## LIMITATIONS OF CT COLONOGRAPHY

Patients are still required to restrict their diet and undergo a bowel cleansing regimen prior to the CT study, similar to colonoscopy, and this can be difficult to complete or may be perceived as an unpleasant experience. Patients may experience abdominal discomfort because of a distended colon during and immediately after the CT examination. The diagnostic ability of CT colonography examinations is dependent on adequate distension and cleansing of the colon. Therefore, detection rates are limited in the setting of suboptimal distension or poor colonic cleansing. Although CT colonography has excellent ability to detect large polyps and cancer, it has poor sensitivity for the detection of small polyps and flat lesions.

Radiologists need additional training to interpret CT colonography studies. Although the axial images are familiar to radiologists, the endoscopic view is a new visualization technique that requires training. A standardized cost needs to be established for CT colonography; the cost must be significantly lower than colonoscopy in order to make this technique available to the greatest number of patients for colorectal cancer screening.

## FUTURE DIRECTIONS

Areas of research include the evaluation of alternative displays that allow the radiologist to view larger areas of the colonic surface at one time. A "virtual pathology" view splits the colon along its longitudinal axis, opening the colon so that it may be inspected like a surgical pathologic specimen. Maplike projections of the colon are also under investigation. The accuracy of these novel visualization methods needs to be determined. Computer-aided detection (CAD) of colorectal lesions is also being studied as a way to shorten interpretation times. Automated polyp detection computer software is under development. The applicable computer algorithms are based on the differences in curvature between polyps and folds or stool.

Fecal and fluid tagging protocols are being evaluated as a way to eliminate the need for cathartic bowel cleansing. Patients ingest positive oral contrast that tags residual material in the colon. This can then be combined with specific computer software that can electronically subtract the labeled material, leaving the colon effectively cleansed.

### See Also the Following Articles

**Colonic Ulcers • Colonoscopy • Colorectal Cancer Screening • Colorectal Adenocarcinoma • Colorectal Adenomas • Computed Tomography (CT) • Sigmoidoscopy**

### Further Reading

Beaulieu, C. F., Jeffrey, Jr., R. B., Karadi, C., Paik, D. S., and Napel, S. (1999). Display modes for CT colonography. Part II. *Radiology* 212, 203–212.

Dachman, A. H., Kuniyoshi, J. K., Boyle, C. M., *et al.* (1998). CT colonography with three-dimensional problem solving for detection of colonic polyps. *AJR Am. J. Roentgenol.* 171, 989–995.

Fenlon, H. M., Nunes, D. P., Schroy, P. C., Barish, M. A., Clarke, P. D., and Ferrucci, J. T. (1999). A comparison of virtual and conventional colonoscopy for the detection of colorectal polyps. *N. Engl. J. Med.* 341, 1496–1503.

Ferrucci, J. T. (2001). Colon cancer screening with virtual colonoscopy: Promise, polyps, politics. *AJR Am. J. Roentgenol.* 177, 975–988.

Fletcher, J. G., Johnson, C. D., Welch, T. J., MacCarty, R. L., Ahlquist, D. A., Reed, J. E., Harmsen, W. S., and Wilson, L. A. (2000). Optimization of CT colonography technique: Prospective trial in 180 patients. *Radiology* 216, 704–711.

Hara, A. K., Johnson, C. D., MacCarty, R. L., and Welch, T. J. (2000). Incidental extracolonic findings at CT colonography. *Radiology* 215, 353–357.

Hara, A. K., Johnson, C. D., MacCarty, R. L., Welch, T. J., McCollough, C. H., and Harmsen, W. S. (2001). CT colonography: Single-versus multi-detector row imaging. *Radiology* 219, 461–465.

Morrin, M. M., Kruskal, J. B., Farrell, R. J., Goldberg, S. N., McGee, J. B., and Raptopoulos, V. (1999). Endoluminal CT colonography after an incomplete endoscopic colonoscopy. *AJR Am. J. Roentgenol.* 172, 913–918.

Summers, R. M., Beaulieu, C. F., Pusanik, L. M., Malley, J. D., Jeffrey, R. B., Glazer, D. I., and Napel, S. (2000). Automated polyp detector for CT colonography: Feasibility study. *Radiology* 216, 284–290.

Yee, J., Akerkar, G. A., Hung, R. K., Steinauer-Gebauer, A. M., Wall, S. D., and McQuaid, K. R. (2001). Colorectal neoplasia: Performance characteristics of CT colonography for detection in 300 patients. *Radiology* 219, 685–692.

Zalis, M. E., and Hahn, P. F. (2001). Digital subtraction bowel cleansing in CT colonography. *AJR Am. J. Roentgenol.* 176, 646–648.

# Vitamin A: Absorption, Metabolism, and Deficiency

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**provitamin A carotenoids** A subset of carotenoids, which are a class of compounds synthesized by plants and microorganisms generally containing eight isoprenoid units, that can be oxidatively metabolized to produce retinal and retinoic acid and cleavage products known as apocarotenoids.

**retinoids** Naturally occurring compounds with vitamin A activity and synthetic analogues with or without vitamin A activity. These include analogues such as isotretinoin (13-*cis*-retinoic acid) that are used medically to treat acne.

**retinyl esters** Fatty acid conjugates of retinol that are the primary storage form of vitamin A in animal tissues.

**vitamin A** Fat-soluble substances that possess the biological properties of the prototypic vitamin A compound, all-*trans*-retinol, which is an unsaturated isoprenoid alcohol with five conjugated all-*trans* double bonds. Other important naturally occurring examples include retinal and retinyl esters. Dietary retinol and retinyl esters are referred to as preformed vitamin A.

**Vitamin A is an essential nutrient that is required for normal growth, epithelial differentiation, fetal development, vertebrate morphogenesis, spermatogenesis, night vision, and a variety of other functions. Vitamin A also has an immunoregulatory role. Many of the actions of vitamin A are mediated by nuclear retinoic acid receptors that can bind to all-*trans*- or 9-*cis*-retinoic acid and act as transcriptional regulators to modulate gene expression. Although all-*trans*- and 9-*cis*-retinoic acid are vitamin A metabolites that mediate most of the biological actions of vitamin A, they are not sufficient for normal spermatogenesis or vision. There is great interest in the mechanisms of vitamin A action, the mechanisms of vitamin A absorption, and factors affecting its bioavailability because vitamin A deficiency remains a major global problem and because retinoids have tremendous potential as therapeutic and chemotherapeutic agents.**

## DIETARY SOURCES OF VITAMIN A

### Animal Sources

Preformed vitamin A (principally retinyl palmitate and smaller quantities of other retinyl esters including stearate, myristate, and oleate) and very small quantities of provitamin A carotenoids are obtained from animal sources. Particularly rich source of preformed vitamin A include liver, whole milk, egg yolks, and fish.

### Plant Sources

Dietary vitamin A is also obtained from plant sources as provitamin A carotenoids. Of the carotenoids, β-carotene is the most abundant. It is efficiently

absorbed and more readily converted to retinol than other carotenoids. Good sources of provitamin carotenoids include carrots, spinach, and other dark-colored fruits and vegetables. These foods also contain carotenoids that cannot be converted to vitamin A but are also thought to have beneficial health effects (e.g., lutein and lycopene).

### Vitamin A Activity of Foods

Retinol activity equivalents (RAE), which correct for the bioavailability of provitamin A carotenoids, are used to compare the vitamin A activity of foods. One RAE is defined as 1 μg of retinol, 2 μg of β-carotene in oil (i.e., as a supplement), 12 μg of β-carotene in food, or 24 μg of other provitamin A carotenoids in foods. One international unit (IU) is equivalent to 0.3 μg of retinol. The recommended daily dietary intakes (RDI) for vitamin A are 900 RAE (3000 IU) and 700 (2333 IU) RAE per day for adult men and nonlactating women, respectively. There is no independent RDI for carotenoids. The Daily Value (DV) of 5000 IU found on food labels in the United States was based on older recommendations. The percentage DV on food labels provides the percentage of the recommended DV (based on a 2000-calorie diet) that is supplied by one serving.

## VITAMIN A ABSORPTION AND METABOLISM

### Digestion and Lumenal Events

Retinyl esters and carotenoids like other water-insoluble lipids are partially released from food by proteolysis and emulsified in the stomach before entering the small intestine. Within the intestinal lumen, retinyl esters are hydrolyzed to retinol and free fatty acids by pancreatic triglyceride lipase, intestinal brush border phospholipase B, and additional retinyl ester hydrolases. With the exception of esterified carotenoids (e.g., xanthophylls), carotenoids are absorbed without prior metabolic conversion within the intestinal lumen. Bile salts are required for the hydrolysis of retinyl esters and for the formation of mixed micelles that facilitate the solubilization of retinol and carotenoids. Following solubilization, retinol is efficiently transported across the brush border at physiological concentrations by a saturable, passive carrier-mediated mechanism. Carotenoids and pharmacological amounts of retinol are absorbed by nonsaturable, non-carrier-mediated, passive mechanisms. Most retinoids are absorbed in the proximal small intestine. The composition of the diet has been shown to affect the bioavailability of vitamin A and carotenoids. With adequate fat intake, 70–90% of preformed vitamin A is absorbed. Carotenoid absorption is particularly dependent on dietary composition and ranges from 5 to 50%. The bioavailability of β-carotene is markedly increased by high-fat diets. The efficiency of vitamin A absorption is diminished in patients with protein energy malnutrition and may be adversely affected by deficiencies in vitamin E and zinc.

### Intracellular Metabolism

Following absorption, retinol, which is poorly soluble in the aqueous cytosol, is bound to the abundant cytosolic cellular retinol-binding protein type II (CRBP II). Most of the CRBP II-bound retinol is reesterified with palmitic acid and other long-chain fatty acids catalyzed by microsomal phosphatidylcholine-retinol *O*-acyltransferase (also known as lecithin:retinol acyltransferase), whereas unbound retinol can be esterified by retinol *O*-fatty-acyltransferase (acyl-CoA-retinol acyltransferase). CRBP II-bound retinol is also a substrate for retinol dehydrogenases that catalyze the reversible oxidation of retinol to retinal, which in turn can be irreversibly oxidized by retinal dehydrogenases to retinoic acid. The small amounts of retinoic acid that are absorbed or synthesized in the intestine may undergo isomerization or glucuronidation. Most provitamin A carotenoids undergo oxidative cleavage to produce apo-carotenoids and retinal, which can be converted to retinoic acid or retinol. β-Carotene can be cleaved centrally to produce two molecules of retinal. In some species, small quantities of carotenoids are exported without modification (e.g., humans and ferrets but not rats and pigs).

### Extraintestinal Metabolism

Most of the retinyl esters, carotenoids, and apocarotenoids are packaged in chylomicron particles for secretion into intestinal lacteals. Retinoic acid and retinoic acid glucuronidates are absorbed via the portal circulation. Metabolism of chylomicrons by plasma lipoprotein lipase in the capillary endothelium produces remnants enriched in vitamin A as well as cholesterol ester and phospholipids. In addition to the liver, which is the major destination and storage site for vitamin A, chylomicron remnants are delivered to the lungs, kidneys, adipose tissue, muscles, spleen, and bone marrow. Within hepatocytes, retinol is reesterified with long-chain fatty acids for storage in sinusoidal stellate cells. Mobilization of hepatic retinyl ester stores is regulated to maintain serum retinol levels within a narrow range. Retinol generated by hydrolysis of retinyl esters is secreted from hepatocytes or stellate cells bound in a

complex to serum retinol-binding protein and transthyretin for delivery to target tissues. Within target tissues, cellular retinol-binding proteins homologous to intestinal CRBP II direct the metabolism of retinol along the same metabolic pathways utilized in the intestine. Carotenoids are cleaved to produce retinal, which is predominantly reduced to retinol, with smaller amounts oxidized to form retinoic acid. The discovery that carotenoid cleavage enzymes are located in extraintestinal tissues including the eye, kidney, testes, brain, and liver indicates that carotenoids can be direct sources of vitamin A and retinoic acid in these tissues. The oxidative inactivation of retinoic acid is mediated by cytochrome P450-dependent enzymes present in the liver and other tissues including skin, lung, and brain. The catabolism of retinoids produces polar metabolites that are excreted into the bile and urine. Although retinoyl and retinyl glucuronides and other retinoids excreted in the bile can be reabsorbed by the small intestine, the physiological significance of the enterohepatic circulation is not known.

## VITAMIN A DEFICIENCY

Disorders that cause generalized fat malabsorption such as chronic pancreatitis and cystic fibrosis and those that result in decreased intestinal absorptive area such as Crohn's disease can result in vitamin A malabsorption and deficiency. Vitamin A deficiency resulting from dietary insufficiency is a major problem in developing nations. Chronic alcoholism is a more frequent cause in industrialized nations. Night blindness is the most sensitive indicator of deficiency in humans. Hypovitaminosis A is also associated with growth retardation, conjunctival xerosis, corneal damage, and impaired immune responses (e.g., mortality from measles is significantly increased in deficient children). Subclinical vitamin A deficiency (i.e., decreased vitamin A stores without overt signs of deficiency) is more prevalent than outright deficiency and may increase susceptibility to intestinal and respiratory infections and impair bone growth in children.

## VITAMIN A TOXICITY

Symptoms of acute vitamin A toxicity resulting from the ingestion over a short period of time of large quantities of preformed vitamin A (>660,000 IU) include nausea and vomiting, vertigo, headache, and blurred vision. Chronic ingestion of vitamin A supplements or fortified foods exceeding three times the RDI leads to hypervitaminosis A. Symptoms include bone and muscle pain, alopecia, anorexia, visual impairment, and hyperlipidemia. Hepatomegaly is common and, particularly in the setting of alcoholism, hepatotoxicity can lead to venoocclusive disease or cirrhosis. Osteoporotic fractures are more common in postmenopausal women who chronically ingest a diet high in preformed vitamin A. Retinoic acid and synthetic retinoids used for medicinal purposes are highly teratogenic during the first trimester. Hypercarotenemia resulting from excessive intake of carotenoids causes yellow discoloration of the skin but is not associated with known toxicities.

### See Also the Following Articles

**Dietary Reference Intakes (DRI): Concepts and Implementation • Malabsorption • Malnutrition**

### Further Reading

Blomhoff, R. (ed.) (1994). "Vitamin A in Health and Disease," Dekker, New York.

Food and Nutrition Board, Institute of Medicine (2002). Vitamin A. *In* "Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc," pp. 82–161. National Academy Press, Washington, DC. Available at http://books.nap.edu/books/0309072794/html/82.html.

Harrison, E. H., and Hussain, M. M. (2001). Mechanisms involved in the intestinal digestion and absorption of dietary vitamin A. *J. Nutr.* 131, 1405–1408.

Levin, M. S. (1994). Intestinal absorption and metabolism of vitamin A. *In* "Physiology of the Gastrointestinal Tract" (L. R. Johnson, ed.), 3rd Ed., Vol. 2, pp. 1957–1978. Raven Press, New York.

Sporn, M. B., Roberts, A. B., and Goodman, D. W. (eds.) (1994). "The Retinoids: Biology, Chemistry and Medicine," 2nd Ed. Raven Press, New York.

# Vitamin $B_{12}$: Absorption, Metabolism, and Deficiency

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**cobalamin analogues** Corrinoids free from any vitamin activity.

**haptocorrin** Corrinoid binding protein, also named R binder, present in the digestive tract and the blood; the functions are not clearly established and may include the clearance of cobalamin analogues from blood.

**intrinsic factor** Glycoprotein secreted by the stomach; binds specifically to cobalamin prior to the receptor-mediated uptake of the intrinsic factor–cobalamin complex in the ileum.

**transcobalamin** Specific blood transport protein that delivers cobalamin to cells by a receptor-mediated endocytosis.

**vitamin $B_{12}$** Micronutrient that belongs to the family of corrinoids; present in animal-derived alimentary tracts and synthesized only by microorganisms. $B_{12}$ corresponds to several vitamers named cobalamins, including deoxyadenosylcobalamin, the cofactor of methylmalonyl-CoA mutase, and methylcobalamin, the cofactor of methionine synthase.

**Vitamin $B_{12}$ (a cobalamin) is synthesized by a wide variety of microorganisms, including telluric bacteria and bacteria from the rumen and the intestine. Foods of animal origin (meat, liver, kidney, eggs, milk, fish, and shellfish) contain vitamin $B_{12}$, which is the only organic molecule to incorporate an atom of cobalt and to contain a ribonucleotide with a 5,6-dimethylbenzimidazole base. As cofactors of methionine synthase and methylmalonyl-coenzyme A mutase, cobalamins play a key role in homocysteine metabolism, energy metabolism, and DNA replication. Severe cobalamin deficiency causes macrocytic and/or megaloblastic anemia with leukoneutropenia and thrombocytopenia, digestive mucosa atrophy, and neurological symptoms such as psychiatric, cognitive, and proprioceptive disorders, related in part to demyelination.**

## PROTEINS INVOLVED IN VITAMIN $B_{12}$ ASSIMILATION AND METABOLISM

Proteins involved in assimilation and activity of the cobalamin vitamin $B_{12}$ (Fig. 1) include intrinsic factor, intrinsic factor receptor, transcobalamin, transcobalamin receptors, and haptocorrin.

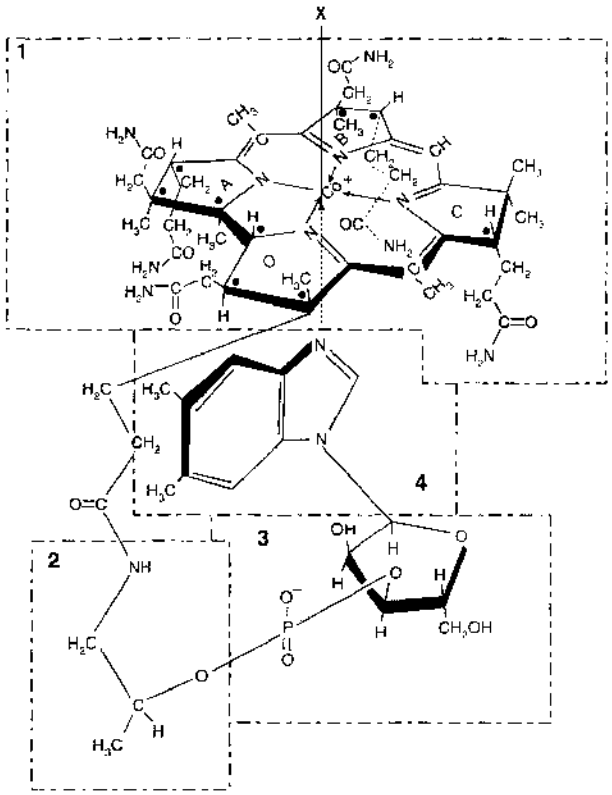


**FIGURE 1** Cobalamin structure. (1) Tetrapyrrole group; (2) amino-1-propanol-2; (3) ribose-3′-phosphate group; (4) 5,6-dimethylbenzimidazole group; X represents a hydroxyl, methyl, 5′-desoxyadenosyl cyanide, or sulfuryl group.

### Intrinsic Factor

Intrinsic factor (IF) is synthesized in humans by the parietal cells of the fundus (fornix; upper area of the stomach) and the gastric body (area of the stomach above the angulus). IF secretion is considerably greater than human daily requirements for IF and occurs by a process closely dependent on membrane translocation. The human gene encoding IF is situated in chromosome 11. The N-lactosaminic and O-glycosidic glycans of the carbohydrate core of IF constitute

 

9.2–15% of the molecule. Removing the carboxyl terminus of the molecule results in all cobalamin (Cbl) binding activity being lost; the amino terminus is important in the conformational changes required for receptor binding. It is possible that there exists an IF "pocket" that could accept the Cbl nucleotide and at least one pyrrole side chain.

### Intrinsic Factor–Cobalamin Receptor

In the human intestine, the greatest amount of the intrinsic factor–cobalamin receptor (IFCR) seems to occur in the final 60 cm of the ileum. IFCR is also expressed in the kidney, in the adult and fetal intestine and colon, in the visceral yolk sac and the placenta, and in HT29 and Caco-2 adenocarcinoma cell lines. Calcium is involved in IFCR oligomerization and IF–Cbl binding is inhibited by wheat germ agglutinin. A 460-kDa multiligand protein named cubilin binds to IF–Cbl and also to apolipoprotein A-I (apoA-I), albumin, and immunoglobulin light chains. It has been concluded that cubilin and IFCR are identical, despite different physicochemical properties, which may be explained by a specific proteolytic cleavage in the intestine. Cubilin is a peripheral membrane protein without a clear membrane-spanning domain, suggesting the requirement for a third protein in the endocytosis mechanism.

### Transcobalamin

Transcobalamin (TC) is a 43-kDa nonglycosylated protein synthesized in most tissues and encoded by a gene located on chromosome 22. It binds to Cbl with a high affinity and delivers blood Cbl to cells by receptor-mediated endocytosis. A low concentration of holo-TC in serum is an indicator of inadequate dietary intake or impaired assimilation. The synthesis of TC increases in inflammatory as well as in neoplastic disorders. A single nucleotide polymorphism in codon 259 affects the blood concentration of the two corresponding isoproteins and behaves as a genetic determinant of homocysteine. Alternative cleavage of the signal peptide also generates two TC isoforms.

### Transcobalamin Receptors

The receptor monomer is present as a dimer in the plasma membrane and is up-regulated by cell proliferation. Uptake of TC–Cbl has been demonstrated in the liver, kidney, heart, spleen, intestine, and lung. A distinct receptor, megalin, is a 600-kDa multiligand protein expressed in the proximal tubules of the kidney and also in other absorptive epithelia. Receptor-mediated endocytosis of TC–Cbl by megalin may account for the accumulation of Cbl in the kidney.

### Haptocorrin

The glycoprotein haptocorrin (HC) carries Cbl and other corrinoids. In the digestive tract, it is secreted in saliva, bile, and pancreatic fluid. It is also expressed in epithelial and glandular cells and granulocytes. Haptocorrin accounts for more than 50% of Cbl bound in gastric juice and 80% in serum. The haptocorrin carbohydrate core represents 30–40% of the molecule and protects part of the molecule from intraluminal proteolysis. The role of haptocorrin in Cbl metabolism is unclear. It may participate in regulating bacterial growth in secretion fluids and in clearing blood Cbl analogues in bile. Asialo-haptocorrin is involved in the liver and intestinal uptake of corrinoids via the receptor of asialoglycoproteins. Although lysosomes are the usual end point for the endocytic pathway for ligands bound to this receptor, HC escapes unaltered into bile by a transcytotic mechanism.

## ASSIMILATION AND METABOLISM OF VITAMIN $B_{12}$

### Intraluminal Stage

Cobalamin bound to dietary food products is released via sequential exposure to heat from cooking and to hydrochloric acid-dependent peptic digestion. The Schilling test, performed with orally ingested radiolabeled Cbl (incorporated in a dietary item such as trout or chicken), can be used to detect patients with chronic gastritis, who are unable to release Cbl from its food binders. In gastric juice, ingested Cbl is exposed to both IF and HC, the latter derived mainly from saliva. However, Cbl binds preferentially to HC, due to a higher affinity for this binding protein. Transfer of Cbl from HC to IF will occur in the intestinal lumen, where there is partial digestion of HC and neutralization of chyme. The intraluminal degradation of biliary HC is therefore a key step of an enterohepatic cycle that permits the selective reabsorption of biliary Cbl in the ileum and the elimination of Cbl analogues in the feces, in a form coupled with partially degraded HC.

### Intestinal Parietal Transport

IF–Cbl uptake occurs in humans by a receptor-mediated endocytosis in the distal ileum. The receptor binding requires a neutral pH and the presence of calcium. Most of the studies on intestinal parietal transport (Fig. 2) have been performed with Caco-2 and HT29

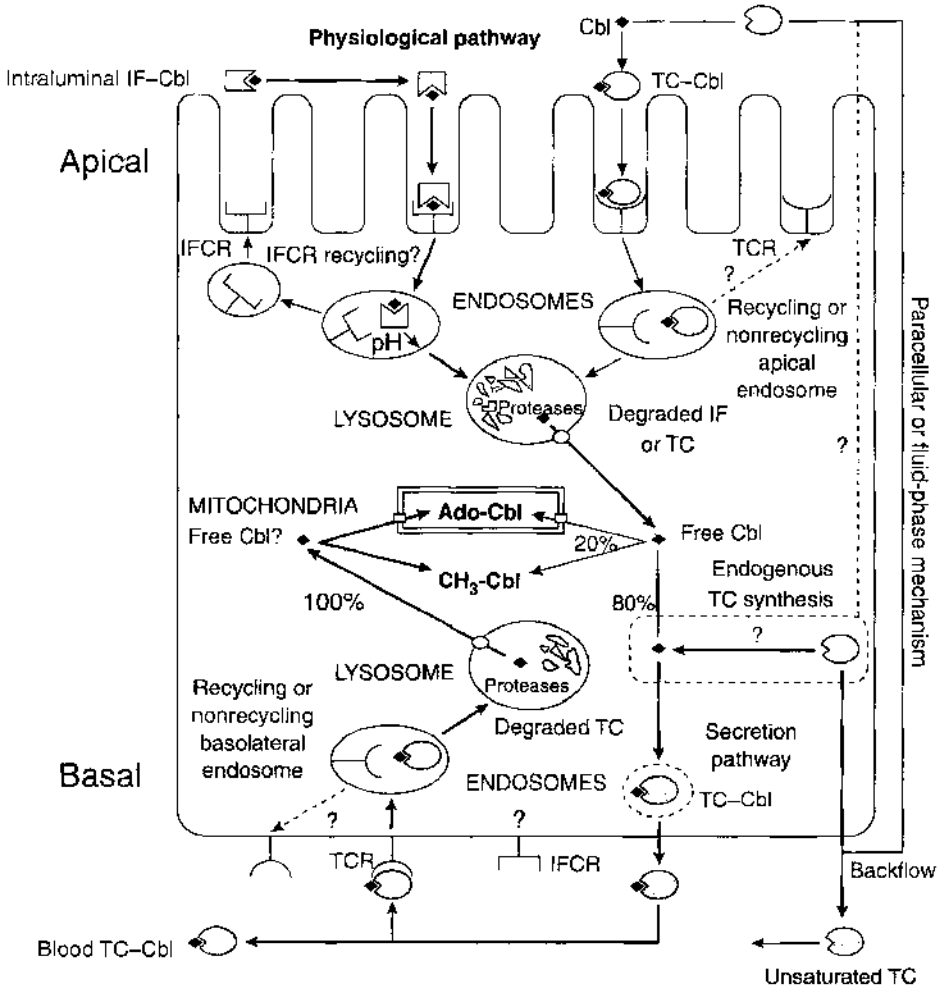


**FIGURE 2** Intestinal parietal transport of vitamin $B_{12}$. The physiological pathway involves the apical intrinsic factor–cobalamin receptor (IFCR)-mediated endocytosis of intrinsic factor–cobalamin (IF-Cbl), release of cobalamin and transfer to endogenous transcobalamin (TC), and basolateral sorting of TC- cobalamin (TC-Cbl). Blood cobalamin can be internalized via a transcobalamin receptor (TCR)-mediated endocytosis of TC -Cbl, on the basolateral side and also on the apical side of Caco-2 cells.

cells. The IF–Cbl complex is dissociated from its apical receptor in early endosomes, under the effect of acid pH. IF is degraded by leupeptin-sensitive proteases such as cathepsin L and by glycosidases. Lysosomes play a key role in free Cbl release to the cytoplasm. Part of the apically transported dietary Cbl can be directly transformed into coenzymes by the enterocyte for its own metabolism. The Cbl sorting to the basolateral side requires the transfer of Cbl to TC in a still unknown cell compartment. The pathways of Cbl receptor-mediated endocytosis are similar in the apical and basolateral sides, except that IF and TC receptors are expressed mainly in the apical and the basolateral sides, respectively. In addition to the TC–Cbl receptor, megalin has been shown to bind to TC–Cbl and mediate its endocytosis. Colocalization of cubilin with megalin in both intestinal and renal epithelia suggests that megalin may be involved in the cell trafficking of IF–Cbl–cubilin. Because of its apical expression in the kidney proximal tubules, renal megalin may function in the tubular reabsorption of TC–Cbl, thus preventing Cbl loss in the urine.

## Intracellular Metabolism

After endocytosis of blood TC–Cbl, the TC receptor is dissociated from the TC–Cbl complex in endosomes and TC is degraded and Cbl is released in lysosomes. In the cytoplasm, cobalamin undergoes reduction from cob(III)alamin to cob(II)alamin, which can then be

methylated to form $CH_3$-Cbl and assist in the methionine synthase conversion of homocysteine to methionine. Alternatively, cob(III)alamin or cob(II)alamin can enter the mitochondria, be further reduced to cob(I) alamin, adenosylated to Ado-Cbl, and participate in the conversion of methylmalonyl-CoA to succinyl-CoA by methylmalonyl-CoA mutase.

## ETIOLOGIES OF VITAMIN $B_{12}$ DEFICIENCY

### Dietary $B_{12}$ Deficiency

The required dietary allowance of vitamin $B_{12}$ has been recently estimated to 2.4 μg/day in adults. An inadequate dietary intake of cobalamin can be observed in vegans and in breast-feeding infants of either vegan mothers or mothers with previously undiagnosed pernicious anemia. However, a vegetarian diet causing $B_{12}$ deficiency is uncommon in western countries, because many foods are fortified with vitamin $B_{12}$.

### Addison's Anemia and Chronic Atrophic Gastritis

Addison's anemia is a type A gastritis; it is also referred to as pernicious anemia or as Biermer's anemia in European countries. It usually occurs in patients aged 60 years or older, may be genetically determined, and is slightly more common in women than in men. Addison's anemia is frequently associated with other diseases, such as Hashimoto's thyroiditis, adrenocortical insufficiency, hemolytic anemia, primary biliary cirrhosis, diabetes, vitiligo, and hypogammaglobulinemia. In addition to megaloblastic anemia, biological data include a low serum Cbl concentration, an abnormal Schilling test that can be corrected in the presence of IF, a drastic reduction in gastric acid and IF secretion, and the presence of serum anti-IF antibodies (which is pathognomonic of the illness) and antiparietal cell autoantibodies in 60% and 80–90% of cases, respectively. There are two types of anti-IF autoantibodies, those that prevent Cbl–IF from binding to its receptor and those that block Cbl from IF binding. The autoantibodies recognize an area of IF that includes the sequence encompassing residues 251–265. A particular clinical form of pernicious anemia occurs in young patients, usually between the ages of 10 and 20 years, and is very often associated with autoimmune outbreaks and a family history.

### Juvenile Pernicious Anemia

Juvenile pernicious anemia is a quite distinct entity. It occurs during the early years of life and may affect several members of a sibling group. Acidic secretion is normal. IF is absent from the gastric juice and there are no serum anti-IF autoantibodies. The presence of degradable IF in neutralized gastric juice has been described in two twins. In another case, IF could not bind to the ileal receptor.

### Protein-Bound Cobalamin Malabsorption

Protein-bound cobalamin malabsorption is a type of deficiency that is sometimes difficult to distinguish from genuine Addison's anemia. It is caused partly by a failure to release dietary Cbl from its protein medium, even if IF secretion is sufficient to enable its absorption. Achlorhydria sometimes causes bacterial overgrowth, which accentuates Cbl malabsorption.

### Gastrectomy

Total gastrectomy is inevitably accompanied by Cbl deficiency, because IF secretion is lacking. Cbl deficiency manifests when the body's reserves are exhausted, i.e., about 3–7 years after gastrectomy. Malabsorption is found in 19–30% of cases of partial gastrectomy. The pathogenesis involves a deficiency of IF and proton secretion, with malabsorption of protein-bound Cbl and blind-loop syndrome.

### Exocrine Pancreatic Insufficiency

Malabsorption of crystalline Cbl may be partly the result of a lack of haptocorrin degradation due to inadequate secretion of pancreatic proteases. However, exocrine pancreatic insufficiency is rarely associated with a Cbl deficiency.

### Obstructive Jaundice

The Schilling test reveals malabsorption of crystalline Cbl in about 40% of cases of obstructive jaundice and in about 50% of patients with external bile drainage. Interruption of bile drainage provides secondary correction. Bile appears to have an effect on binding of the Cbl–IF complex with the ileal receptor.

### Bacterial Overgrowth

An imbalance of the intestinal flora, known as blind-loop syndrome, occurs in various pathological circumstances, including Finsterer- or Polya-type gastrectomies, segmentary intestinal resection with end-to-side anastomosis, ileocolic resection, inflammatory intestinal diseases, diverticulosis, or gastric achlorhydria. Bacteria possess binding sites that can trap Cbl after

bacterial proteases and glycosidases act to dissociate the IF–Cbl complex.

### Tropical Sprue

The mechanism involved in $B_{12}$ deficiency in tropical sprue may involve the intraluminal and parietal phases of Cbl assimilation. Cbl malabsorption can be reversed by antibiotic treatment over a period of time.

### Parasitic Infestations

The main parasites involved in $B_{12}$ deficiency are *Diphyllobothrium latum* (causing diphyllobothriasis, or fish tapeworm) and *Giardia lamblia* (lambliasis); fish tapeworm infestation, however, is now only anecdotal. Infection is accompanied by a decrease in IF secretion and atrophic gastritis. The parasite traps Cbl bound with IF as well as free Cbl. In cases of lambliasis, malabsorption is primarily the result of Cbl being trapped by the parasite, but also the result of mucosal alteration.

### Zollinger–Ellison Syndrome

In Zollinger–Ellison syndrome, hypergastrinemia is accompanied by hyperacidity and irreversible inactivation of pancreatic lipase in the duodenum, producing luminal lipase deficiency.

### Malabsorption of Iatrogenic Origin

Long-term treatment with proton pomp inhibitors such as omeprazol may occasionally produce a Cbl deficiency related to inadequate assimilation of protein-bound Cbl. Cholestyramine is a resin that can chelate IF by ion exchange. Colchicine, alcohol, and antibiotics can act as inhibitors of IF–Cbl endocytosis. Occasionally, patients with undiagnosed vitamin $B_{12}$ deficiency who have received nitrous oxide anesthesia may experience neurologic abnormalities in the weeks after the exposure.

### Congenital Defects of $B_{12}$ Assimilation

A small number of cases with congenital deficiency of IF have been reported. Mutations appear to be both structural and regulatory. One patient had a combined deficiency of IF and HC, suggesting a genetic linkage between regions located on chromosome 11 that encode the two proteins. Three siblings in one family had an abnormal IF that was markedly susceptible to gastric acid and to proteolytic enzymes. The selective intestinal malabsorption of Cbl, also known as the Gräsbeck–Imerslund syndrome or megaloblastic anemia 1 (MGA1), is a rare autosomal recessive disease, often associated with a proteinuria independent of Cbl deficiency. The pathogenesis may correspond to a defect of expression, stability, and/or trafficking of IFCR. Abnormal binding of IF–Cbl to the receptor has been found in ileum biopsies and urine assays of patients. Two cubilin gene mutations, FM1 and FM2, have been identified in some (not all) MGA1 patients.

### Inherited Defects of $B_{12}$ Blood Transport

Inherited TC deficiency manifests in the first few month of life. Most of the 30 known patients lack immunologically detectable TC. Two deletion mutations have been detected in the TC gene of one patient. Because of the role of TC in blood transport and ileal transcytosis of Cbl, its absence impairs Cbl absorption as well as cell delivery.

### Inherited Defects of $B_{12}$ Cellular Metabolism

Patients with deficiencies in intracellular cobalamin metabolism and utilization have been classified by fibroblast complementation analysis into eight groups. Patients who have defects in methionine synthase (MS) (*cblG*) or in the regeneration of methylcobalamin (MeCbl) (*cblE*) have homocystinuria and hyperhomocysteinemia. Those who have defects in the mutase ($mut^0$, $mut^-$) or in the formation of deoxyadenosylcobalamin (AdoCbl) (*cblA*, *cblB*) have methylmalonic aciduria and methylmalonic acidemia. Patients with blocks in the early steps of cobalamin cellular transport cannot synthesize MeCbl or AdoCbl (*cblC*, *cblD*, *cblF*), which results in a combined increase of homocysteine and methylmalonic acid.

## TREATMENT OF VITAMIN $B_{12}$ DEFICIENCY

Intramuscular injections of vitamin $B_{12}$ (usually 1000 µg/month) have been the classic treatment for vitamin $B_{12}$ deficiency. High-dose oral vitamin $B_{12}$ pills and injections of $B_{12}$ have the same efficiency for curing megaloblastic anemia and neurologic disorders. Patients can be managed with oral doses of 300–2000 µg/day.

### See Also the Following Articles

**Cobalamin Deficiency • Dietary Reference Intakes (DRI): Concepts and Implementation • Intrinsic Factor • Malnutrition • Pernicious Anemia**

## Further Reading

Alpers, D. H. (1999). Intrinsic factor, haptocorrin and their receptor. *In* "Chemistry and Biochemistry of B12" (R. Banerjee, ed.), pp. 411–440. John Wiley & Sons, New York.

Christensen, E. I., and Birn, H. (2002). Megalin and cubilin: Multifunctional endocytic receptors. *Nat. Rev. Mol. Cell Biol.* 3, 256–266.

Guéant, J. L. (1990). Malabsorption of cobalamins. *In* "Cobalamin and Related Binding Proteins in Clinical Nutrition" (J. L. Guéant and J. P. Nicolas, eds.), pp. 55–68. Elsevier, Amsterdam.

Pons, L., Guy, M., Lambert, D., Hatier, R., and Guéant, J. L. (2000). Transcytosis and coenzymatic conversion of ($^{57}$Co) cobalamin bound to either endogenous transcobalamin II or exogenous intrinsic factor in Caco-2 cells. *Cell Physiol. Biochem.* 10, 135–148.

Rosenblatt, D. S. (1999). Inborn errors of cobalamin metabolism. *In* "Chemistry and Biochemistry of B12" (R. Banerjee, ed.), pp. 367–384. John Wiley & Sons, New York.

Rothenberg, S. P., Quadros, E. V., and Regec, A. (1999). Transcobalamin II. *In* "Chemistry and Biochemistry of B12" (R. Banerjee, ed.), pp. 441–473. John Wiley & Sons, New York.

Seetharam, B. (1999). Receptor-mediated endocytosis of cobalamin (vitamin B12). *Annu. Rev. Nutr.* 19, 173–195.

# Vitamin K: Absorption, Metabolism, and Deficiency

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menaquinone Vitamin $K_2$.
phylloquinone Vitamin $K_1$.

**Vitamin K was discovered more than 50 years ago following investigation of a hemorrhagic disease in cattle and chicks that was corrected by vitamin K dietary supplements. The vitamin's name stems from the German word *Koagulationsvitamin*. Vitamin K and its derivatives have a 2-methyl-1,4-naphthoquinone nucleus with a lipophilic side chain at position 3. This lipophilic chain gives vitamin K its unique properties. The most abundant form of vitamin K is phylloquinone (vitamin $K_1$), which is found in green leafy vegetables and certain plant oils. Another form, menaquinone (vitamin $K_2$), has several subtypes; some are synthesized by the intestinal microflora (subtypes MK-7, MK-8, MK-10, and MK-11) and other nutritionally significant variants (MK-4) occur only in meats (especially liver). In contrast to vitamin $K_1$, the contribution of vitamin $K_2$ to human nutrition is poorly understood.**

## ABSORPTION

Most of the absorption of vitamin K occurs in the distal small intestine. Dietary phylloquinone is protein bound and requires pancreatic enzymes for liberation into the lumen of the small intestine. The highly lipophilic cleaved products are solubilized into micelles by bile and are absorbed into the lymphatic circulation after being incorporated into chylomicrons. Ultimately, these chylomicrons enter the portal circulation and reach the liver by a carrier-dependent process. When the intraluminal levels of bile salts fall below the critical micellar concentration required for absorption, deficiency of vitamin K and other fat-soluble vitamins is likely to develop. Therefore, vitamin K absorption depends on the functional integrity of the liver, small intestine, and pancreas.

## METABOLISM

In humans, vitamin K functions as a cofactor for the endoplasmic enzyme γ-glutamylcarboxylase. This enzyme is involved in a unique posttranslational carboxylation reaction, in which glutamate residues on various proteins are converted into γ-carboxyglutamate (Gla). This reaction occurs during the last stages of protein synthesis. The resulting Gla residues are characteristic

of a limited number of proteins found in liver, bone, and blood vessels.

Vitamin K occurs naturally in the quinone oxidized state and is reduced to the hydroquinone form (vitamin $KH_2$) by the enzyme vitamin K epoxide reductase (VKOR). In turn, vitamin $KH_2$ becomes the active cofactor for the vitamin K-dependent enzyme γ-glutamylcarboxylase. Vitamin $KH_2$ is oxidized to vitamin K 2,3-epoxide (KO). Indeed, this reaction provides the energy driving the carboxylation reaction by the vitamin K-dependent γ-glutamylcarboxylase. Under normal conditions, for each molecule of Gla generated, one molecule of vitamin K epoxide is also formed. There is a strict one-to-one stoichiometric relation between the conversion of vitamin $KH_2$ to KO and the number of protein bound Gla residues formed.

After protein degradation, Gla residues are excreted in urine. It is clear that the number of carboxylation reactions far exceeds the number of vitamin K molecules available. The short-lived, highly reactive epoxide (KO) is potentially toxic and is recycled back to vitamin $KH_2$ by the enzyme VKOR. Warfarin inhibits VKOR, which leads to insufficient generation of vitamin $KH_2$ by interrupting the recycling of vitamin $K_2$ (see Fig. 1). This results in a vitamin K-depleted state, leading to clinical manifestations and raising the nutritional requirement. In such situations, a second enzyme, NAD(P)H dehydrogenase [also known as detoxifying (DT) diaphorase], reduces quinone to vitamin $KH_2$ but not the epoxide (KO). Interruption of this cycle leads to production of decarboxyglutamate. Measurement of proteins containing decarboxyglutamate gives an early indication of vitamin K deficiency.

Vitamin K plays a major role in the synthesis of clotting factors. The Gla-containing coagulation proteins promoting clotting include prothrombin and factors VII, IX, and X. Vitamin K is also involved in the biosynthesis of the antithrombotic proteins C and S. With the exception of protein S (produced in many tissues), all these proteins are exclusively synthesized in the liver.

Abnormal bleeding is a cardinal sign of vitamin K deficiency. The function of Gla residues on blood coagulation proteins is to facilitate adhesion to the negatively charged phospholipids on the surface of activated platelets. Gla residues, along with calcium, are internalized to the core, leading to exposure of the phospholipid binding domains.

Other important Gla-containing proteins, such as protein Z, osteocalcin, and matrix growth protein (MGP), are involved in equally important metabolic functions. Protein Z helps thrombus adherence to sites of injury. Osteocalcin is a product unique to bone tissue produced by osteoblasts, the deficiency of which may be related to development of osteoporosis. MGP play a crucial role in bone formation and in addition to protein S contributes to maintaining vascular stability. All Gla-containing proteins are synthesized in the endoplasmic reticulum in a propeptide form. The propeptide contains the γ-carboxylation recognition site characteristic of the vitamin K-dependent proteins, except in MGP, where this site resides in the mature protein.

## DEFICIENCY

The dietary requirement for vitamin K is approximately 100–200 μg/day and the current recommended daily allowance is 65–80 μg/day, in addition to the estimate for what is produced by colonic synthesis. Vitamin K deficiency in an otherwise healthy adult is rare. Acquired deficiency can occur in patients on long-term antibiotics and parenteral nutrition or with gastrointestinal diseases characterized by maldigestion, malabsorption, hepatobiliary disease (diminished hepatocellular function or cholestasis), and other disease states. Salicylates, anticonvulsants, and large doses of vitamin E (> 1200 IU/day) have been associated with

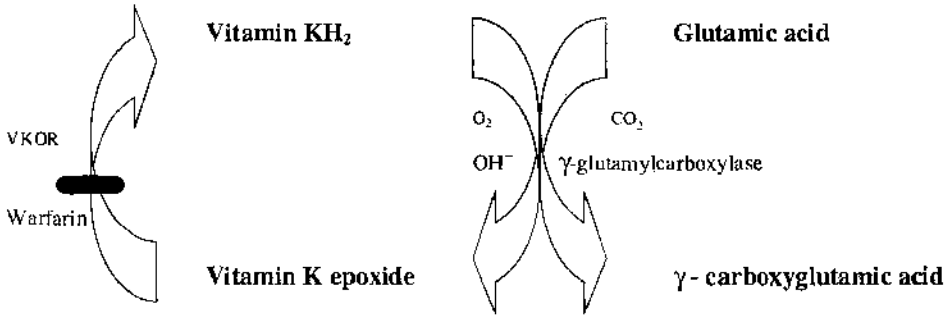


FIGURE 1 Biosynthetic pathway for vitamin K-dependent production of γ-carboxyglutamic acid. Warfarin inhibits the enzyme vitamin K epoxide reductase (VKOR).

vitamin K deficiency in some patients. A state of therapeutic deficiency is induced by administration of coumadin-based anticoagulants. An important acquired vitamin deficiency state is hemorrhagic disease of the newborn. The normal newborn has a moderate deficiency of vitamin K-dependent coagulation factors. Adult levels are achieved at about 3 months of age. Hemorrhagic disease of the newborn is now uncommon due to routine administration of vitamin K at birth.

Vitamin K status can be determined by various methods. Until recently, direct measurement of vitamin K was difficult. Plasma phylloquinone levels can now be measured directly by high-pressure liquid chromatography. Plasma levels of vitamin K primarily reflect dietary intake over the previous 24 hours. In addition to direct measurement of plasma phylloquinone level, vitamin K status can be measured by indirect methods. A widely used indicator is the determination of the prothrombin time (PT), which becomes prolonged in vitamin K deficiency. PT is nonspecific for vitamin K deficiency because it also becomes prolonged in hepatocellular dysfunction and certain hematological disorders (coagulopathies). The specificity of PT can be increased by the so-called vitamin K test. In this test, reversal of prolonged PT by parenteral vitamin K administration confirms vitamin K deficiency caused by inadequate dietary intake or intestinal malabsorption. Improvement of the PT after parenteral vitamin K is less consistent with coagulopathy of parenchymal hepatocellular disease. Improvement of PT is noted within 8 hours, with a maximum improvement at 48 hours. Absence of improvement or a minimal change in PT suggests investigating hepatocellular causes of prolonged PT.

In emergencies, vitamin K can be administered by slow intravenous injection, but there is risk of arterial hypotension and rarely anaphylaxis. Intramuscular injection is not generally recommended. The PT test can respond rapidly to changes in levels of factor VII, which has a half-life of only 4–7 hours. However, PT is considered relatively insensitive for detecting vitamin K deficiency because it becomes prolonged when factor VII levels fall below 40%. PT is even less sensitive to prothrombin concentration, becoming prolonged only when prothrombin levels fall below 30% of normal. Another indirect method to assess vitamin K status involves measurement of decarboxylated osteocalcin. This substance would appear a relatively sensitive indicator of vitamin K deficiency, because its affinity for γ-glutamylcarboxylase is lower than that of other vitamin K-dependent proteins. Therefore, detection of decarboxylated osteocalcin may provide an early indication of mild vitamin K deficiency.

## See Also the Following Articles

Dietary Reference Intakes (DRI): Concepts and Implementation • Malnutrition • Parenteral Nutrition • Small Intestine, Absorption and Secretion

## Further Reading

Booth, S. L., and Saltzman, E. (2001). *In* "Rakel: Conn's Current Therapy," 53rd Ed., pp. 609–611. W. B. Saunders, Philadelphia.

Food and Nutrition Board, Institute of Medicine (2001). Panel on micronutrients, Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. National Academy Press, Washington, D.C.

Furie, B., Bouchard, B. A., and Furie, B. C., (1999). Vitamin K-dependent biosynthesis of gamma carboxyglutamic acid. *Blood* 93(6), 1798–1808.

Grosset, A. B. M., and Rodgers, G. M. (1998). *In* "Wintrobe's Clinical Hematology," 10th Ed., Vol. 2, pp. 1733–1767. Williams and Wilkins, Philadelphia.

Rutherford, C. J., and Frenkel, E. P. (1999). *In* "Diseases of Liver" (E. R. Schiff, M. F. Sorrell, and W. C. Maddrey, eds.), 8th Ed., Vol. 1, pp. 583–596. Lippincott-Raven, Philadelphia.

Veermer, C., and Schurgers, L. J. (2000). A comprehensive review of vitamin K and vitamin K antagonists. *Hematol. Oncol. Clin. North Am.* 14(2), 339–353.

# Volvulus

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**closed-loop obstruction** Type of mechanical obstruction in which both the proximal and distal segments of bowel are obstructed.

**volvulus** Abnormal twisting of a segment of bowel, resulting in a mechanical obstruction of the proximal and distal parts of the involved segment.

**Volvulus is an important cause of acute intestinal obstruction in infants and of gastric and intestinal obstruction in adults. Volvulus, defined as an abnormal twisting of a segment of bowel, results in a mechanical obstruction of the proximal and distal segments of the involved bowel. The resultant closed-loop obstruction has a particularly high risk of strangulation, necrosis, and perforation. The anatomic requirements underlying the development of volvulus include a redundant segment of bowel that is freely moveable within the peritoneal cavity, with close approximation to the points of fixation of the bowel.**

## GASTRIC VOLVULUS

### Anatomy and Etiology

The stomach is fixed inferiorly by the duodenum, and its normal orientation is maintained by the gastrosplenic, gastroduodenal, gastrophrenic, and gastrohepatic ligaments. About two-thirds of cases of gastric volvulus are associated with a congenital or acquired diaphragmatic hernia in which the stomach (or part of the stomach) is positioned within the chest. One-third of cases of gastric volvulus occur below the diaphragm and are due to laxity of the ligamentous attachments of the stomach to the duodenum, liver, spleen, and diaphragm. Sliding paraesophageal hernias are not associated with gastric volvulus because the stomach maintains its normal configuration as part of it ascends into the posterior mediastinum.

Gastric volvulus may be classified anatomically as organoaxial or mesenteroaxial, depending on the axis on which the volvulus occurs. Most cases of gastric volvulus are organoaxial in nature, with the stomach twisting on its long axis. This axis most commonly passes through the gastroesophageal and the gastropyloric junctions, with the antrum rotating anteriorly and superiorly and the fundus rotating posteriorly and inferiorly, causing torsion of the greater curvature at a point along its length. This type of gastric volvulus is most often associated with diaphragmatic hernias and causes gastric ischemia and infarction in 5–28% of cases. Mesenteroaxial gastric volvulus occurs when the stomach folds on an axis extending from the lesser to the greater curvature such that the antrum twists anteriorly and superiorly. This type of volvulus occurs in about one-third of cases and is more likely to be incomplete, intermittent, and associated with chronic symptoms.

### Clinical Manifestations

Patients with acute gastric volvulus experience sudden, severe upper abdominal or chest pain. In those cases in which the stomach is located within the abdomen, there is upper abdominal distension. Patients with herniation of the stomach through a diaphragmatic defect present with severe chest pain radiating to the arms and neck with accompanying dyspnea, misleading the unsuspecting clinician into believing the patient may be suffering acute myocardial infarction. Persistent retching productive of little or no vomitus is a common manifestation. The triad of abdominal or chest pain, violent retching, and the inability to pass a nasogastric tube should lead to a strong clinical suspicion of acute gastric volvulus. Patients with chronic gastric volvulus may have mild, nonspecific, or intermittent symptoms such as epigastric discomfort, heartburn, abdominal fullness, or bloating. A large, unusual gas-filled viscus in the chest or upper abdomen on plain abdominal radiograph suggests the diagnosis, which may be confirmed by barium-swallow radiographic study or computed tomography.

### Treatment

Surgical therapy for patients presenting with acute gastric volvulus, after initial resuscitation, involves laparotomy with operative reduction, resection of necrotic tissue, and repair of precipitating conditions such as a

 

hiatal hernia. On occasion, a nasogastric tube may be placed to allow resuscitation and an elective repair, but more frequently a tube cannot be placed and immediate operation is mandatory. Patients presenting with chronic recurrent volvulus should have a careful preoperative identification of precipitating conditions followed by operative repair. In those cases in which primary volvulus occurs without obvious cause, gastropexy may be performed by tacking the anterior wall of the stomach to the parietal peritoneum of the abdominal wall.

## MIDGUT VOLVULUS

The most common form of small bowel volvulus is midgut volvulus.

### Etiology

Midgut volvulus is an important cause of intestinal obstruction in neonates and infants and is caused by incomplete (or absent) rotation of the embryonic intestine during the fifth to twelfth week of gestation. From 50 to 75% of cases are discovered in the first month of life and 90% of cases are detected before 1 year of age.

The most common abnormality associated with midgut volvulus is nonrotation, in which there is inadequate counterclockwise rotation of the midgut loop around the superior mesenteric artery (SMA). This causes the duodenojejunal junction to be located to the right of the midline, as is the remainder of the small intestine. The colon resides in the left abdomen with the cecum near the midline. A narrow mesenteric pedicle predisposes to volvulus, and the peritoneal attachments (Ladd's bands), which extend anterior and lateral to the duodenum to fix the cecum to the posterior body wall, may obstruct the duodenum.

### Clinical Presentation

The discovery of malrotation during infancy occurs when duodenal obstruction from Ladd's bands or midgut volvulus develops. Infants with duodenal obstruction from Ladd's bands present with proximal duodenal obstruction and bilious vomiting with little abdominal distension. Midgut volvulus may also present with obstructive symptoms; however, the development of intestinal ischemia due to strangulation may cause transmural necrosis with acidemia, thrombocytopenia, and sepsis.

### Diagnosis

The high risk of intestinal ischemia and necrosis from midgut volvulus and the associated very high mortality rate mandate aggressive diagnosis and management of neonatal intestinal obstruction. A plain abdominal radiograph in babies with midgut volvulus will demonstrate a distended stomach and proximal duodenal bulb with a paucity of small bowel gas. An upper gastrointestinal contrast study will be diagnostic by demonstrating malpositioning of the duodenojejunal junction to the right of the midline, with the small intestine on the right and the cecum and ascending colon to the left. The contrast study may also demonstrate a characteristic corkscrew or coiled appearance in the third or fourth portions of the duodenum. A barium enema demonstrating the cecum in the right lower quadrant does not exclude the possibility of malrotation and midgut volvulus.

### Treatment

The treatment of intestinal malrotation, whether manifested by duodenal obstruction from Ladd's bands or midgut volvulus, is operative. In the latter case, the diagnosis should be followed by laparotomy because a delay of even hours may mean the difference between viable or gangrenous bowel. Operative repair of malrotation is achieved by the Ladd procedure, which consists of relief of the volvulus and division of the peritoneal bands tethering the cecum, small bowel mesentery, mesocolon, and duodenum around the base of the superior mesenteric artery. This allows the mesenteric leaves to open widely and is associated with a very low incidence of recurrent volvulus. Meticulous and complete mobilization of the entire duodenum with division of all anterior, lateral, and posterior peritoneal attachments relieves the extrinsic compression and obstruction of the distal duodenum.

## COLONIC VOLVULUS

Volvulus causes about 10–15% of all colonic obstructions in the United States and other Western countries and about 1–4% of all cases of intestinal obstruction. In Eastern Europe and parts of Africa and Asia, colonic volvulus accounts for 20–50% of all intestinal obstructions. It is the second most common cause of colonic obstruction, the most common being adenocarcinoma. The sigmoid colon and cecum are the most frequent sites of colonic volvulus, accounting for about 75 and 22% of all cases, respectively. Rare sites for colonic volvulus include the transverse colon (2%) and splenic flexure (<1%).

## Etiology and Pathophysiology

In each case, a freely mobile segment of intra-abdominal colon twists or folds on fixed afferent and efferent limbs of the bowel, causing a closed-loop obstruction. As fluid and gas accumulate within the involved segment of bowel, intraluminal pressure rises, and when it exceeds capillary pressure, the colonic wall becomes ischemic. Closed-loop obstructions, such as that occurring with colonic volvulus, are associated with a high rate of ischemia, infarction, and perforation.

## Clinical Presentation

The most common clinical manifestations of colonic volvulus are acute abdominal distension and lower abdominal pain. When present, the pain varies from a vague discomfort accompanying abdominal distension to the excruciating pain of peritonitis. Severe unremitting pain suggests gangrenous bowel and peritonitis. The duration of symptoms in patients with sigmoid volvulus is often less than that in patients with malignant or benign strictures. Abdominal tenderness occurs in less than one-third of patients with colonic volvulus. Patients with sigmoid volvulus are often in the seventh or eighth decade of life and often have various comorbid illnesses. A history of chronic constipation and laxative use is also a frequent finding in patients with cecal or sigmoid volvulus. Patients with cecal volvulus tend to be younger than patients with sigmoid volvulus and have a history of prior abdominal operations or distal obstruction. The most common physical finding is massive abdominal distension, which is always present. Significant abdominal tenderness with evidence of peritonitis suggests impending or actual colonic necrosis and perforation and mandates emergent operative intervention.

## Diagnostic Evaluation

The initial diagnostic approach to patients suspected of having colonic obstruction includes plain abdominal radiographs in the supine and upright positions. The abdominal radiograph of patients with sigmoid volvulus will demonstrate a markedly dilated sigmoid colon and proximal bowel with minimal gas in the rectum. The standard radiographic appearance of sigmoid volvulus is a distended ahaustral sigmoid loop, i.e., "bent inner-tube" appearance; the apex of which is directed toward the right shoulder. The classic radiographic features of cecal volvulus include (1) a massively dilated cecum located in the epigastrium or left upper quadrant, (2) a kidney bean shape of the distended cecum, (3) distended loops of small bowel, suggesting small bowel obstruction, and (4) a single, long air- fluid level present on upright or decubitus films. In these instances, the massively distended cecum extends across the abdominal midline and is "directed" toward the left upper quadrant or left midabdomen. These "classic" radiographic findings are seen in 40–60% of cases.

The remaining diagnostic studies in patients with colonic obstruction are predicated on the presence or absence of peritonitis and the degree of obstruction (i.e., partial or complete). Patients with peritonitis should undergo resuscitation and urgent laparotomy without further diagnostic procedures, whereas patients without evidence of bowel wall ischemia and an abdominal radiograph suggestive of a distal complete obstruction should undergo proctosigmoidoscopy. This procedure will demonstrate the site and nature of distal strictures and in the case of sigmoid volvulus may allow decompression.

If the obstruction is proximal to the area visualized by proctosigmoidoscopy, a water-soluble contrast enema will confirm the diagnosis of colonic obstruction and delineate the site of obstruction. In patients with sigmoid or cecal volvulus and an equivocal plain abdominal radiograph, a water-soluble contrast enema may be helpful by demonstrating a point of torsion (e.g., a mucosal spiral pattern, or "bird's beak" sign). The use of water-soluble contrast media obviates the risk of barium impaction at the site of obstruction and barium peritonitis in the case of unrecognized perforation.

Although colonoscopy may be useful in patients with partial colonic obstruction, it has little role in the initial evaluation of patients suspected of having complete obstruction. The insufflation of air or carbon dioxide through the endoscope into the obstructed bowel may exacerbate colonic distension and precipitate perforation.

## Treatment and Outcome

Resuscitation of patients with colonic obstruction includes restoration of intravascular volume, correction of electrolyte abnormalities, and nasogastric aspiration. The urgency with which the obstruction must be decompressed is dependent on the degree of obstruction (partial or complete) and the clinical presentation of the patient (evidence of strangulation or not). As alluded to earlier, the initial management of patients with sigmoid volvulus without evidence of peritonitis is proctoscopic decompression of the obstruction, often assisted by placing a rectal tube into the obstructed bowel. In a compilation of 19 American series including 595 patients with sigmoid volvulus, Ballantyne reported that

proctoscopy, either alone or combined with a rectal tube, successfully reduced the volvulus in 70–80% of attempts. The placement of a rectal tube for 48 hours may minimize the possibility of early recurrence. Successful reduction of sigmoid volvulus has also been reported with flexible sigmoidoscopy or colonoscopy; however, the procedure must be performed with limited manipulation and minimal insufflation of air or carbon dioxide.

The risk of recurrence following nonoperative reduction of a sigmoid volvulus is 40–50%. Thus, following proctoscopic decompression, the patient should undergo mechanical cleansing of the bowel, followed by elective sigmoid resection. This multistep approach allows time for optimization of the patient's condition prior to laparotomy, resection, and the performance of a primary anastomosis. Recurrence rates following this approach are less than 3%. Patients requiring emergent laparotomy for strangulated sigmoid volvulus require sigmoid resection with an end colostomy and Hartmann pouch.

The role of initial nonoperative management of patients with cecal volvulus is less well defined than that of sigmoid volvulus. Although colonoscopy has been successfully employed to reduce the volvulus, the risk of perforation of the thinned, often ischemic, cecum is substantial, as is the danger of missing a segment of necrotic bowel with delay of definitive resection. Current options for the operative management of cecal volvulus include cecopexy, cecostomy, and resection. Detorsion alone or when combined with appendectomy is associated with a high recurrence rate. In some cases, the performance of a cecopexy, in which the right colon is anchored to the peritoneum of the right paracolic gutter with or without a cecostomy, is favored. Right colectomy with primary ileotransverse colostomy effectively prevents recurrent volvulus and is the procedure of choice of a number of surgeons, including the authors. Ballantyne reported 27 patients with cecal volvulus who were treated with resection and primary anastomosis with no operative mortality and no recurrence of volvulus in 5 years of followup.

Overall, the mortality rate for patients with colonic volvulus is about 8%, with the major predictive factor for mortality being the presence of gangrenous bowel. The incidence of gangrenous bowel in patients with either cecal or sigmoid volvulus is 15–20%. In a review of 18 American studies including 299 patients with sigmoid volvulus, the mortality rate for patients with gangrenous colons was 80%, whereas only 10% of patients without colonic necrosis died.

## See Also the Following Articles

**Colectomy • Colonic Obstruction • Duodenal Obstruction • Gastric Volvulus • Gastrostomy • Malrotation**

## Further Reading


Agrez, M., and Cameron, D. (1981). Radiology of sigmoid volvulus. *Dis. Colon Rectum* **24**, 510.

Anderson, J. R., and Welch, G. H. (1986). Acute volvulus of the right colon: An analysis of 69 patients. *World J. Surg.* **10**, 336.

Ballantyne, G. H. (1982). Review of sigmoid volvulus: History and results of treatment. *Dis. Colon Rectum* **25**, 494.

Ballantyne, G. H. (1982). Review of sigmoid volvulus: Clinical patterns and pathogenesis. *Dis. Colon Rectum* **25**, 823.

Ballantyne, G. H., Brandner, M. D., Beart, R. W., Jr., *et al.* (1985). Volvulus of the colon: Incidence and mortality. *Ann. Surg.* **202**, 83.

Brothers, T. E., Strodel, W. E., and Eckhauser, F. E. (1987). Endoscopy in colonic volvulus. *Ann. Surg.* **206**, 1.

Burke, J. B., and Ballantyne, G. H. (1984). Cecal volvulus: Low mortality at a city hospital. *Dis. Colon Rectum* **27**, 737.

Carter, R., Brewer, L. A., and Hinshaw, D. B. (1980). Acute gastric volvulus. *Am. J. Surg.* **140**, 99.

Grossman, E. M., Longo, W. E., Stratton, M. D., *et al.* (2000). Sigmoid volvulus in Department of Veterans Affairs Medical Centers. *Dis. Colon Rectum* **43**, 414.

Haskin, P. H., Teplick, S. K., Teplick, J. G., *et al.* (1981). Volvulus of the cecum and right colon. *J. Am. Med. Assoc.* **245**, 2433.

Turnage, R. H., and Bergen, P. (2002). Intestinal obstruction and ileus. *In* "Sleisinger's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management," (M. Feldman, L. S. Friedman, and M. H. Sleisinger, eds.), 7th Ed., pp. 2113–2128. W. B. Saunders, Philadelphia.

W

# Water-Soluble Vitamins: Absorption, Metabolism, and Deficiency

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**adaptive regulation** A process by which a transport event is up- or down-regulated by conditions in the surrounding environment, such as the level of a particular substrate in the diet or in the extracellular fluid.

**carrier-mediated membrane transport** Mechanism for transporting a substrate that involves a defined protein system located at the plasma membrane of the cell.

**ontogenic regulation** A process describing developmental changes, for example, in a transport event.

**transport by passive diffusion** A process by which a solute moves from one side of the membrane to the other without the need for a specialized transporting system.

**vitamin suboptimal level** Level of the vitamin that falls below the normal range.

The water-soluble vitamins are a structurally unrelated group of organic compounds that share the same features of being essential for normal cellular functions, growth, and development and exist in minute quantities in the diet. Humans and other mammals obtain these micronutrients from exogenous sources (e.g., diet) via intestinal absorption. Thus, the intestine plays a central role in the regulation of normal body homeostasis of these nutrients. As a result, deficiency and suboptimal levels of these nutrients occur in a variety of disease conditions and states that affect the intestine. This includes both inherited defects in the intestinal transport systems involved and secondary causes such as intestinal diseases (e.g., inflammatory bowel disease, celiac disease), excessive alcohol intake, drug interactions, intestinal resection, and aging. This article will provide a brief description of the metabolic role of these nutrients and the current understanding of their intestinal absorption mechanisms and regulation.

## VITAMIN B1

### Metabolic Role and Deficiency

Vitamin B1 (thiamine), in its pyrophosphate form, plays a critical role in normal carbohydrate metabolism, participating in the decarboxylation of pyruvic and α-ketoglutamic acids and in the utilization of pentose in the hexose monophosphate shunt. Thiamine deficiency in humans leads to a variety of clinical abnormalities including neurological (neuropathy and/or Wernicke-Korsakoff syndrome) and cardiovascular disorders (e.g., peripheral vasodilation, biventricular myocardial failure, edema, and potentially acute fulminant cardiovascular collapse). Thiamine deficiency represents a significant nutritional problem in both developed and underdeveloped countries. In developed countries, thiamine deficiency has been reported in a high percentage of alcoholics, in diabetics, in patients with renal diseases, acquired immunodeficiency syndrome, cancer, celiac disease, and congestive heart failure, and in those on long-term use of the diuretic furosemide. Thiamine deficiency also occurs in thiamine-responsive megaloblastic anemia due to a genetic defect in the thiamine transport system SLC19A2. Furthermore, deficiency of thiamine has been reported in the elderly despite an average daily intake of the vitamin that exceeds the recommended requirement.

### Intestinal Thiamine Absorption

Humans and other mammals cannot synthesize thiamine and thus must obtain the vitamin from exogenous sources via intestinal absorption. The intestine is exposed to two sources of thiamine: a dietary source and a bacterial source (the latter is via synthesis of the vitamin by the normal microflora of the large intestine). Previous studies using a variety of human and animal intestinal preparations have established the involvement of a specialized, carrier-mediated mechanism for thiamine uptake in the small intestine. This includes studies with intestinal biopsies, surgical specimens, purified jejunal brush border membrane vesicles isolated from human organ donors, and cultured human-derived intestinal epithelial cell lines. The identified uptake system was found to transport the vitamin via a proton gradient-dependent exchange mechanism. A similar carrier-mediated thiamine uptake mechanism was also found at the apical membrane of human colonocytes and is believed to be responsible for the uptake

 

of thiamine that is produced by the normal microflora of the large intestine. Following transport into the cell, thiamine is phosphorylated by the action of the cytoplasmic thiamine pyrophosphokinase, a process probably aimed at increasing the retention of the vitamin. It then exits the cell across the intestinal basolateral membrane as free (unphosphorylated) thiamine. The mechanism of transport of thiamine across the human basolateral membrane also occurs via a specialized carrier-mediated mechanism. One of the factors that have been shown to interfere with the normal intestinal thiamine uptake process *in vivo* is excessive alcohol intake. Also, the intestinal thiamine uptake process has been shown to be sensitive to the inhibitory effect of the diuretic amiloride.

### Molecular Identity of the Intestinal Thiamine Transport System(s)

Insight into the molecular identity of the intestinal thiamine transport process has begun to emerge in recent years with the cloning of two human thiamine transporters, SLC19A2 and SLC19A3. Both of these transporters were found to be expressed in the human intestine. In addition, the *SLC19A2* promoter appears to be very active following transfection into intestinal epithelial Caco-2 cells. Although these studies point to the possible involvement of these transporters in intestinal thiamine absorption, further studies are required to establish their relative contribution.

### Regulation of Intestinal Thiamine Uptake

Studies with human-derived cultured intestinal epithelial cells have shown that the thiamine uptake process is under the regulation of an intracellular $Ca^{2+}$–calmodulin-mediated pathway. Also, thiamine deficiency has been reported to up-regulate thiamine uptake by human intestinal biopsy specimens.

## VITAMIN B2

### Metabolic Role and Deficiency

Vitamin B2 (riboflavin), in its coenzyme forms, riboflavin-5′-phosphate (FMN) and flavin adenine dinucleotide (FAD), is involved in many critical metabolic reactions including amino acid, carbohydrate and lipid metabolism and in the conversion of folic acid and pyridoxine into their coenzyme forms. Deficiency of riboflavin in humans leads to a variety of clinical abnormalities including degenerative changes in the nervous system, endocrine dysfunction, anemia, and skin disorders. Riboflavin deficiency and suboptimal levels have been reported in different conditions including alcoholism, patients with diabetes mellitus, inflammatory bowel disease (IBD), or human immunodeficiency virus infection and those receiving chemotherapy.

### Intestinal Riboflavin Absorption

Humans and other mammals have lost the ability to synthesize riboflavin and thus must obtain riboflavin from exogenous sources via intestinal absorption. The intestine is exposed to riboflavin from two sources: the diet and the bacterially synthesized vitamin in the large intestine. Dietary riboflavin exists mainly in the form of FMN and FAD. These forms are hydrolyzed to free riboflavin in the intestinal lumen prior to absorption, a process performed by the action of intestinal phosphatases. The mechanism of absorption of dietary riboflavin has been extensively studied using a variety of human and animal intestinal preparations. These studies have shown the proximal part of the small intestine to be the preferential site of riboflavin absorption. Also, a specialized, carrier-mediated mechanism was found to be involved in riboflavin uptake. The amount of bacterially synthesized riboflavin in the large intestine varies depending on the diet, being higher following consumption of a vegetable-based diet than of a meat-based diet. In addition, the large intestine has been shown to be capable of absorbing a significant amount of lumenally introduced riboflavin. The mechanism of riboflavin absorption in the colon has been studied with cultured human colonic epithelial cells and has been shown to occur via a carrier-mediated system that is similar to that observed in the small intestine. Factors that have been shown to interfere with the normal intestinal riboflavin uptake process include alcohol and certain tricyclic drugs, such as chlorpromazine. Nothing is currently known about the molecular identity of the intestinal riboflavin uptake system.

### Regulation of Intestinal Riboflavin Uptake

The intestinal riboflavin uptake process has been shown to be adaptively regulated by extracellular substrate levels and by specific intracellular protein kinase-mediated regulatory pathways. Oversupplementation with pharmacological amounts of riboflavin has been shown to lead to a significant and specific down-regulation in riboflavin uptake. On the other hand, riboflavin deficiency causes a significant and specific up-regulation in intestinal riboflavin uptake. The latter effect appears to be mediated via an increase in the

number (and/or activity) of the riboflavin uptake carriers with no changes in their affinity. The intestinal riboflavin uptake process was also found to be under the regulation of an intracellular PKA-mediated pathway. This pathway appears to exert its effect via a decrease in riboflavin carrier activity/number. Furthermore, the intestinal riboflavin uptake process was found to be ontogenically regulated during early stages of life.

## VITAMIN B3

### Metabolic Role and Deficiency

The main function of vitamin B3 (also known as niacin or nicotinic acid) is to act as a precursor for the synthesis of two important coenzymes: NAD and NADP. Both of these coenzymes are involved in maintaining the redox state of the cell. Most NAD- and NADP-linked enzymes are involved in catabolic reactions, such as glycolysis and the pentose phosphate shunt. In addition, niacin appears to have a beneficial effect as a lipid-lowering agent. Severe niacin deficiency occur in humans and leads to pellagra, a disease characterized by skin lesions, weight loss, diarrhea, inflammation of mucous membranes, vertigo, and mental confusion. Niacin deficiency occurs in alcoholics and in patients that carry mutations in the tryptophan transport gene (Hartnup's disease). Niacin deficiency occurs in the latter population because tryptophan is a precursor for nicotinic acid production in the body.

### Intestinal Nicotinic Acid Absorption

The body obtains niacin from two sources: endogenously via conversion of tryptophan to niacin, a process that occurs mainly in the liver and kidneys, and exogenously from the diet via intestinal absorption. Limited studies regarding the cellular and molecular aspects of intestinal niacin absorption are available. Uptake studies have shown the involvement of a carrier-mediated, pH-dependent uptake system for nicotinic acid in mammalian intestine. The reported pH dependence of intestinal nicotinic acid uptake process is in contrast to the reported sodium dependency of the vitamin uptake process in renal epithelial cells. Some of the internalized nicotinic acid undergoes metabolism to intermediates of the Preiss-Handler pathway for NAD biosynthesis. Nothing is currently known about the cellular regulation of the intestinal nicotinic uptake process.

## VITAMIN B6

### Metabolic Role and Deficiency

Vitamin B6 consists of a group of structurally related micronutrients (pyridoxine, pyridoxal, and pyridoxamine) that exist in both unphosphorylated and phosphorylated forms. Pyridoxal phosphate is the most biologically active derivative and functions as a cofactor in several enzymatic reactions including those involved in amino acid metabolism. Vitamin B6 deficiency leads to a variety of clinical abnormalities including peripheral neuritis, depression, confusion, and dermatitis. Deficiency and/or suboptimal levels of vitamin B6 occur in alcoholics, patients with renal disease, diabetics, those on long-term use of certain medications (e.g., isoniazid and other hydrazines), and those with B6-responsive anemia.

### Intestinal Vitamin B6 Absorption

Humans and other mammals cannot synthesize vitamin B6 and thus must obtain the vitamin via intestinal absorption. Dietary phosphorylated forms of vitamin B6 are hydrolyzed in the intestinal lumen prior to absorption. Absorption of the unphosphorylated vitamin B6 has been reported to occur via a nonsaturable simple diffusion process. Following absorption, the various components of vitamin B6 accumulate within the absorptive cell, primarily in the phosphorylated form. The phosphate esters then are dephosphorylated over time, with final transfer of the products to the circulation across the basolateral membrane. Although vitamin B6 status was found to be regulated homeostatically, this does not appear to be due to alterations in intestinal absorption of the vitamin.

## VITAMIN B12

Vitamin B12 will be discussed only briefly here.

### Metabolic Role and Deficiency

Vitamin B12 (also known as cobalamin, Cbl) is important for maintaining the normal differentiation, proliferation, and metabolic status of all cells. It acts as a coenzyme for two key enzymatic reactions: the conversion of homocysteine to methionine and the conversion of methylmalonyl coenzyme A (coA) to succinyl coA. Deficiency of Cbl leads to intracellular accumulation and eventual secretion into the plasma of the metabolites of these two reactions, homocysteine and methylmalonic acid. Elevated plasma levels of these two metabolites are a strong indication of an intracellular

deficiency of Cbl. Intracellular Cbl deficiency can arise due to multiple causes that include both acquired and inherited disorders. Strict vegetarians and vegans develop Cbl deficiency due to a lack of intake, and patients with tapeworm infestation or bacterial overgrowth develop Cbl deficiency due to competition for dietary Cbl. These patients can be treated successfully with adequate intake of Cbl when the underlying cause is eliminated with antibiotics. However, patients with gastric surgery (partial or complete) or surgery of the ileum (chronic inflammation) will develop Cbl deficiency as they will not be able to absorb Cbl due to decreased levels or total loss of intrinsic factor or the ileal receptor, respectively. In these patients, along with children who have inherited disorders involving intrinsic factor, its ileal receptor, or the plasma transporter transcobalamin II or a number of defects that involve its intracellular utilization, deficiency of Cbl is permanent and must be treated on a regular basis with intramuscular injections of pharmacological doses of Cbl. Another factor that interferes with intestinal Cbl absorption in humans is excessive ethanol consumption.

### Intestinal Cobalamin Absorption

Humans and other mammals must obtain Cbl from the diet because they cannot synthesize the vitamin. After digestion, free Cbl binds to a hydrophobic protein ligand, the gastric intrinsic factor (IF), prior to absorption. Cbl bound to the IF is then endocytosed via a distinct cell surface receptor, the intrinsic factor–cobalamin receptor (also called cubilin), located at the brush border membrane of distal ileum epithelia. In humans, IF is localized mainly to the parietal cells, but it is also detected at the margins of the anatomical regions in clusters of chief cells, enteroendocrine cells, and endothelial cells. IF is a glycoprotein with one Cbl-binding site. It is believed that the carbohydrate moiety of IF affords protection from proteolytic degradation. This is not too surprising considering the ability of IF to remain structurally and functionally intact even after its exposure to proteases of the stomach and intestinal lumen. Following endocytosis of the IF–Cbl complex, the IF portion is degraded. This is followed by intracellular formation of a transcobalamin II–Cbl complex and release into circulation across the basolateral membrane.

## VITAMIN C

### Metabolic Role and Deficiency

Vitamin C (ascorbic acid) is required by all cells; it functions as a powerful antioxidant, assists in maintaining metal ions in their reduced forms, and plays a role in a variety of hydroxylation reactions. Vitamin C deficiency leads to scurvy, a disease that is primarily due to an abnormality in collagen formation that leads to, among other things, bleeding from the gums and joint, muscle, and dystrophic hair deformities. The incidence of vitamin C deficiency or scurvy is rare in developed countries and usually occurs in certain populations at risk, such as individuals with alcoholism and the elderly.

### Intestinal Vitamin C Absorption

Primates and guinea pigs are the only mammals that cannot synthesize ascorbic acid from glucose endogenously and thus have a dietary requirement for the vitamin and obtain it via intestinal absorption. Dietary vitamin C occurs in two forms: the reduced form (i.e., ascorbic acid, AA) and the oxidized form (i.e., dehydroascorbic acid, DHAA). Intestinal absorption of AA has been the subject of extensive investigations using a variety of human and animal intestinal preparations. Uptake was found to occur without significant metabolic alterations in the transported substrate and to involve a specialized, $Na^+$-dependent, carrier-mediated system that is localized at the apical membrane of the absorptive enterocytes. Exit of AA from the enterocyte across the intestinal basolateral membrane occurs via a $Na^+$-independent carrier-mediated system.

As to DHAA, the amount of this form of the vitamin in the human diet is not fully documented but it is likely to increase during prolonged storage of food. The intestinal absorptive cells are capable of taking up DHAA and metabolizing it to the reduced ascorbic acid. The mechanism of uptake of DHAA across the intestinal brush border membrane appears to be via a $Na^+$-independent transport process. This process is believed to involve the mammalian facilitative hexose transporters and appears to represent a physiologically significant pathway for uptake and accumulation of vitamin C by many different cells.

### Molecular Identity of Ascorbic Acid Transport System(s)

Two $Na^+$-dependent L-ascorbic acid transporters, the so-called sodium-dependent vitamin C transporters 1 and 2 (SVCT1 and SVCT2, respectively), have been cloned and shown to be expressed in intestinal absorptive cells. The level of expression of SVCT1 is markedly higher than that of SVCT2, and SVCT 1 appears to play a more important role in the overall intestinal AA absorption process. Both transporters have higher selectivity

for L-ascorbic acid than for D-isoascorbic acid and dehydroascorbic acid; also, they both transport L-ascorbic acid via an electrogenic $Na^+$-dependent process (stoichiometric ratio of 2 : 1 for $Na^+$ to ascorbic acid). SVCT1 was found to share 65% identity with SMVT2 at the amino acid level, but no identity was found between these two transporters and other mammalian membrane transporters.

### Regulation of Intestinal AA Uptake

Animal studies have shown that the process of intestinal AA uptake is down-regulated following oversupplementation of the vitamin. No information, however, exists as to the molecular mechanism(s) involved in this adaptive regulation.

## BIOTIN

### Metabolic Role and Deficiency

Biotin acts as a coenzyme for four carboxylases that are essential for gluconeogenesis, the metabolism of several branched-chain amino acids, and fatty acid synthesis. Deficiency of biotin leads to serious clinical abnormalities, which include neurological disorders, growth retardation, and dermal abnormalities. Also, at least in animals, biotin deficiency during pregnancy leads to embryonic growth retardation, congenital malformation, and death. The incidence of biotin deficiency and suboptimal conditions has been reported with increased frequency in recent years. Biotin deficiency has been reported in patients with inborn errors of biotin metabolism, in patients on long-term therapy with anticonvulsant agents, and in patients on long-term parenteral nutrition. Suboptimal biotin levels have also been reported during pregnancy, in substantial numbers of alcoholics, in patients with inflammatory bowel diseases, and in infants with seborrheic dermatitis and Leiner's disease.

### Intestinal Biotin Absorption

Mammalian cells cannot synthesize biotin and thus must obtain the vitamin from exogenous sources via absorption in the intestine. The intestine is exposed to two sources of biotin: a dietary source and a bacterial source (the latter being via synthesis of the vitamin by the normal microflora of the large intestine). Dietary biotin exists in free and protein-bound forms. The latter form is digested first by gastrointestinal proteases and peptidases to generate biocytin (*N*-biotinyl-L-lysine) and then is converted to free biotin by the action of the enzyme biotinidase. The mechanism of absorption of free biotin in the small intestine has been studied using a variety of human and animal intestinal preparations. These studies have shown the involvement of a specialized, $Na^+$-dependent carrier-mediated mechanism for biotin uptake across the intestinal brush border membrane. At the basolateral membrane, biotin was found to exit the cell via a $Na^+$-independent carrier system. In adult humans, biotin uptake is significantly higher in the duodenum and jejunum than in the ileum. Recently, it has been recognized that the intestinal biotin transport system also transports the structurally and functionally unrelated water-soluble vitamin pantothenic acid and the metabolically important substrate lipoate. Thus, a new name was given to the transport system: the sodium-dependent multivitamin transporter (SMVT). The nutritional consequences of competition between these vitamins for a common transporter are not currently known. As to transport of the bacterially synthesized biotin in the large intestine, an efficient $Na^+$-dependent, specialized, carrier-mediated system (similar to that of the small intestine) has been identified in human colonocytes. Among the factors that have been shown to negatively interfere with the normal intestinal biotin transport process are the long-term use of certain anti-epileptic medications (Primidone and Tegretol) and alcohol intake.

### Molecular Identity of the Intestinal Biotin Transport System(s)

The molecular identity of the intestinal biotin transport system, SMVT, was delineated following cloning of its cDNA from a number of species including humans and rats. At least in rats, significant heterogeneity was found in the 5′-untranslated region of the SMVT cDNA, with four distinct variants (I, II, III, and IV) being identified. Variant II was found to be the predominant form expressed in the small and large intestine. Also, villus cells were found to express significantly more SMVT message than crypt cells. Furthermore, the 5′-regulatory regions of the human and rat SMVT genes have been cloned and characterized and multiple promoters that drive transcription of these genes have been identified.

### Regulation of Intestinal Biotin Uptake

The intestinal absorption of biotin was found to be regulated both by extracellular substrate level and by specific intracellular protein kinase-mediated pathways. Biotin deficiency was found to lead to a specific and significant up-regulation in biotin intestinal uptake. On the other hand, oversupplementation with pharmacological doses of biotin was found to lead to a specific and significant down-regulation of

the intestinal biotin uptake. These effects were found to be mediated mainly via changes in the number of the biotin transport carriers. Also, an intracellular protein kinase C and a $Ca^{2+}$/calmodulin-mediated pathway appear to play a role in regulating the intestinal biotin uptake process. Furthermore, the intestinal biotin uptake process was shown to undergo ontogenic regulation during early postpartum development.

## FOLIC ACID

### Metabolic Role and Deficiency

The coenzyme derivatives of the vitamin folic acid (folate) are necessary for the synthesis of purine and pyrimidine precursors of nucleic acids, for the metabolism of certain amino acids, and for the initiation of protein synthesis in mitochondria. Folate deficiency leads to a variety of clinical abnormalities including megaloblastic anemia and growth retardation. Recent studies have also suggested that low folate levels may play a role in the etiology of coronary artery disease (via folate involvement in the metabolism of homocysteine) and colonic, cervical, and lung neoplasia. In contrast to the negative consequences of folate deficiency and suboptimal levels, optimization of folate body homeostasis has been shown to be effective in preventing certain diseases (e.g., prevention of neural-tube defects) and has also been reported to decrease the risk of developing certain types of cancer, most notably in the colon. Folate deficiency is a highly prevalent vitamin deficiency throughout the world. In the Western Hemisphere, a significant number of folate deficiency cases result from impairment in intestinal absorption of the vitamin. This impairment is common in a variety of intestinal diseases (e.g., IBD) and has also been associated with the use of certain pharmacological agents (e.g., sulfasalazine, phenytoin). Furthermore, impairment in intestinal folate absorption due to congenital defects has also been reported.

### Intestinal Folate Absorption

Humans and other mammals cannot synthesize folate and thus must obtain the vitamin via intestinal absorption. The intestine is exposed to folate from two sources: a dietary source, where the vitamin is absorbed in the small intestine, and a bacterial source, where the vitamin is synthesized by normal microflora in the large intestine. The main form of dietary folate is the folate polyglutamate form. This form must be converted to the folate monoglutamate form prior to absorption, a process achieved via the special action of the intestinal folate hydrolase. The absorption of the released folate monoglutamates has been the subject of extensive investigations. These investigations have established that (1) the proximal part of the small intestine is the main site of absorption of dietary folate with significantly less uptake in the ileum; (2) a specialized, carrier-mediated system is involved in folate uptake across the apical membrane of the absorptive cells that transports the vitamin by an electroneutral process; (3) the uptake system is highly dependent on an acidic extracellular pH with significantly less uptake at neutral and alkaline pH; and (4) the uptake system transports reduced (e.g., 5-methyltetrahydrofolate, 5-MTHF), oxidized (e.g., folic acid), and substituted (e.g., the folate analogue methotrexate, MTX) folate derivatives with similar affinities. The last two features of the intestinal folate uptake process are unique to the intestine and are different from the widely characterized folate uptake process of nonpolarized cells, such as that of the mouse leukemia L1210 cells. The intestinal epithelial cells are also unique compared to other absorbing (transporting) epithelial cells such as those of the kidney and the placenta, in that they do not utilize the other folate uptake mechanism via the folate receptor (also known as the membrane folate-binding protein) under normal conditions. The factors that negatively affect intestinal folate absorption are alcohol consumption and the use of certain pharmacological agents, such as sulfasalazine and phenytoin.

As to the bacterially synthesized folate in the large intestine, studies using apical membrane vesicles isolated from the colon of organ donors and cultured human colonic epithelial NCM 460 cells have shown the uptake to be via a specific, carrier-mediated, pH-dependent, uptake mechanism that is sensitive to the effect of the anion exchange inhibitor DIDS. The system appears to be similar (or identical) to that in the small intestine.

### Molecular Identity of the Intestinal Folate Transport System

The molecular identity of the intestinal folate uptake system has also been delineated by cloning its cDNA from human and mouse intestine. The open reading frames of the human and mouse intestinal cDNA clones were found to be very similar (or identical in the case of the mouse) to the open reading frame of the cDNA of the reduced folate carrier cloned from nonpolarized cells of the respective species. This is despite the fact that the characteristics of the folate uptake process in these distinct cell types are different. Subsequent studies have shed some light onto how the reduced folate carrier (RFC) exhibits such different characteristics in distinct cells and suggested that the cell environment may play a role in causing the difference.

### Regulation of Intestinal Folate Uptake

The intestinal folate absorption process appears to be under the regulation of extracellular and intracellular mechanisms. Dietary folate deficiency has been shown to lead to a significant and specific up-regulation in folate uptake. This up-regulation appears to involve transcriptional regulatory mechanisms. Intracellular protein tyrosine kinase- and protein kinase A-mediated pathways have also been reported to play a role in regulating the intestinal folate uptake process. Furthermore, the intestinal folate uptake process was found to undergo ontogenic regulation during the early stages of life.

## PANTOTHENIC ACID

Pantothenic acid is needed for the synthesis of coenzyme A and acyl carrier protein in mammalian cells and thus is important in the metabolism of carbohydrate, fat, and, to a lesser extent, protein. Pantothenic acid deficiency in humans is rare, but its induction leads to depression and fatigue. As with most other water-soluble vitamins, mammals lack the ability to synthesize pantothenic acid and thus must obtain the vitamin from exogenous sources via intestinal absorption. The intestine is exposed to two sources of pantothenic acid: dietary and bacterial. Dietary pantothenic acid exists mainly in the form of coA, which is hydrolyzed to free pantothenic acid in the intestinal lumen prior to absorption. The mechanism of absorption of pantothenic acid in the small intestine involves the same carrier-mediated $Na^+$-dependent system that transports biotin (i.e., SMVT; see Biotin above). Similarly, colonic absorption of pantothenic acid was found to involve the same biotin $Na^+$-dependent, carrier-mediated system. It is worth mentioning that the interaction between biotin and pantothenic acid transport has also been seen in other tissues and organs, such as the blood–brain barrier, the heart, and the placenta. However, the nutritional consequences of such interactions have not been investigated.

## SUMMARY

The water-soluble vitamins are essential for normal human health and well-being. Deficiency of these micronutrients leads to a variety of clinical abnormalities, some of which have been recognized since ancient times. For humans, water-soluble vitamins are obtained from exogenous sources via intestinal absorption. Studies using a variety of human and animal intestinal preparations including intact tissues, cellular preparations, and membrane vesicles have established that for most of these micronutrients, efficient and specialized carrier-mediated transport systems exist. Some of these systems are driven by $Na^+$ gradients, others are driven by $H^+$ and/or $OH^-$ gradients, and yet others are not affected by an ion gradient. In addition, the molecular identity of some of these transport systems has been delineated by cloning and their promoters have been characterized. Furthermore, it is now known that a variety of intestinal diseases and conditions negatively interfere with the normal absorption process of these nutrients and thus warrant closer attention by the treating physician to avoid deficiency and prevent suboptimal levels from occurring.

### Acknowledgments

This work was supported by grants from the Department of Veterans Affairs and the National Institutes of Health (DK56061 and DK58057).

### See Also the Following Articles

**Cobalamin Deficiency • Dietary Reference Intakes (DRI): Concepts and Implementation • Folate Deficiency • Malnutrition • Small Intestine, Absorption and Secretion • Vitamin B12: Absorption, Metabolism, and Deficiency**

### Further Reading

Cooperman, J. M., and Lopez, R. (1984). Riboflavin. *In* "Handbook of Vitamins: Nutritional, Biochemical and Clinical Aspects" (L. J. Machlin, ed.), pp. 299–327. Dekkes, New York.

Said, H. M., Rose, R., and Seetharam, B. (2000). Intestinal absorption of water-soluble vitamins: Cellular and molecular aspects. *In* "Current Topics in Membranes: Gastrointestinal Transport Molecular Physiology" (K. E. Barrett and M. Donowitz, ed.), pp. 35–76. Academic Press, San Diego, CA.

Seetharam, B. (1994). Gastric intrinsic factor and cobalamin absorption. *In* "Physiology of the Gastrointestinal Tract" (L. Johnson, ed.), chap. 62, pp. 1997–2026. Raven Press, New York.

Wrong, O. M., Edmonds, C. J., and Chadwich, V. S. (1981). Vitamins. *In* "The Large Intestine: Its Role in Mammalian Nutrition and Homeostasis," pp. 157–166. Wiley, New York.

# Webs

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**antrum** Distal portion of the stomach between the body and the pylorus.
**atresia** Nondevelopment of an expected structure.
**double-bubble sign** Radiographic appearance signifying duodenal obstruction. Consists of large air collections in the stomach and in the duodenum, without visualization of gas more distally in the gastrointestinal tract.
**duodenum** The first portion of the small intestine, located between the stomach and the jejunum.
**stenosis** Narrowing.
**web** A thin sheet of tissue or large mucosal fold protruding into the lumen of a hollow organ, often causing obstruction.
**windsock** A type of partially obstructing duodenal web that balloons into the more distal duodenum like an internal diverticulum.

**Gastrointestinal webs are an uncommon form of congenital or acquired stenosis found in a variety of locations within the gastrointestinal tract. The webs discussed herein include esophageal, antral, and duodenal webs. They may be congenital or acquired and they present in both adults and children.**

## INTRODUCTION

As outlined above, a gastrointestinal (GI) web is an uncommon finding and can be identified in a number of locations throughout the alimentary tract. This article is concerned with three of the more common GI webs: esophageal, antral, and duodenal. The common clinical presentations, diagnoses, imaging findings, and current therapies will be outlined briefly, though it is important to note that theories of pathogenesis and treatment continue to evolve. Pertinent radiographs will also be included and links with other disorders will be examined.

## ESOPHAGEAL WEBS

Esophageal webs (often equated with rings) may be found as either congenital or acquired lesions. Many can be linked with specific disease states, whereas others are found as isolated lesions. The presentation, diagnosis, and therapy depend on both the putative mechanism and the age of the patient. In general, webs rarely protrude more than 5 mm into the lumen, are eccentrically located, and average 2–4 mm in thickness (Fig. 1). Most are asymptomatic. They can be found anywhere along the esophagus, though most are anterior and posterior to the cricoid. Webs in the upper esophagus are covered with squamous mucosa, whereas those in the lower esophagus are often covered with columnar gastric mucosa. All are believed to contain mucosa and submucosa with scanty muscular fibers.

### Congenital Esophageal Webs

Congenital esophageal webs are relatively uncommon and can be located at any level. If the web is complete and totally excludes the lumen, it will present as a form of esophageal atresia. These are thought to be secondary to failure of recanalization of the primitive

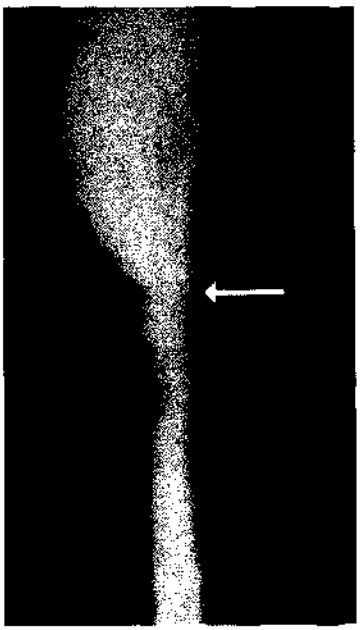

FIGURE 1 Arrow indicates the location of the esophageal web.

 

foregut. Single webs are more common than multiple webs. The prevalence is unknown, but is estimated to be 1 in 25,000–50,000 live births, with females more commonly affected than males. There is no ethnic predilection. Although isolated webs have been reported, they are more likely to occur in conjunction with tracheoesophageal fistulas, Down's syndrome, VACTERAL malformations, and prematurity. Webs severely compromising the lumen are often discovered at birth by inability to pass a suction catheter. Others may not present until later in childhood or adulthood (usually before the age of 40), when inability to feed, vomiting, and aspiration are noted. A web that severely narrows the lumen is not compatible with life and early endoscopic dilation or transthoracic surgical removal is necessary following stabilization of the patient's clinical condition. Diagnosis is most often made by endoscopy. Upper GI studies can also be diagnostic, though there is a real risk of aspiration of the contrast medium.

A special case of congenital webs is the Schatzki ring. Also composed of both mucosa and submucosa, it is typically located at the gastroesophageal junction and is believed to mark the proximal margin of a hiatal hernia. Although some believe that the ring offers protection against gastroesophageal reflux, this is not generally agreed upon. Meat impaction and progressive dysphagia are common, though many adults are asymptomatic. In older patients, gastroesophageal reflux disease (GERD) should be ruled out.

### Acquired Esophageal Webs

Acquired webs, found in both children and adults, are secondary to a variety of causes. Most are postcricoid. The true incidence of acquired webs is unknown, as 95% are asymptomatic. Webs are found in approximately 6–14% of barium examinations of the upper gastrointestinal tract and diagnosis can be made by both upper GI barium study and endoscopy. The common clinical complaint is intermittent dysphagia for solid foods, alternating with long periods of normal swallowing. Dysphagia is most likely if the web narrows the lumen to less than 13 mm in diameter. Acquired esophageal webs can be found associated with chronic GERD, Plummer-Vinson syndrome, hiatal hernias, cicatrious pemphigoid, chronic infection, celiac sprue, connective tissue disorders, or ingestion of corrosive agents. Treatment of the underlying condition, such as correction of the anemia in Plummer-Vinson syndrome or anti-reflux medications in GERD, will often correct the web. If this is not the case, endoscopic dilation or surgical disruption can be performed. Progressive dysphagia or increasing pain should prompt a search for underlying malignancy.

## ANTRAL WEBS

Congenital gastric outlet obstruction resulting from antral webs is quite uncommon and represents less than 1% of stenoses of the alimentary tract. The cause of the defect is unknown, but failure of recanalization of the primitive foregut is again implicated. A small number of nonobstructing webs can be seen in association with conditions such as hypertrophic pyloric stenosis. Sex distribution is approximately equal. Most cases of complete antral webs present on the first day of life with nonbilious vomiting, feeding difficulties, and abdominal distension with no distal gas. Gastric perforation is a real danger. However, the degree of obstruction dictates the severity of symptoms. Older children and adults with less severe narrowing may present with nausea, vomiting, abdominal pain, and weight loss. Diagnosis of an antral web (Fig. 2) is suggested by the findings of a thin persistent septum near the pyloric channel on barium examination. Disruption of peristalsis to the level of the antrum is also suggestive of the diagnosis. Endoscopy can confirm the diagnosis. Treatment of this rare lesion entails correction of metabolic disturbances, as well as nasogastric tube placement. Surgical or endoscopic repair, consisting of simple excision or pyloroplasty, can then be undertaken.

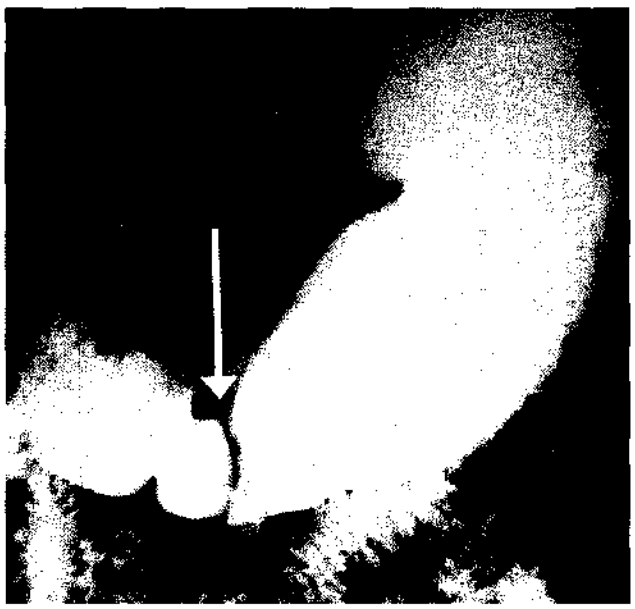

**FIGURE 2** Circumferential narrowing of the gastric antrum by a web (arrow).

## DUODENAL WEBS

As is the case with the esophageal webs discussed above, duodenal webs may form as a result of primary failure of recanalization of the primitive foregut in the fourth to fifth week of development, though this is debated. Nearly all duodenal webs are congenital in origin and nearly all are discovered within a few days of birth, although diagnosis may be delayed until adulthood if the degree of obstruction allows the passage of food. Single webs are more common than multiple webs and are most often found in the first and second portions of the duodenum. Complete duodenal webs are the most common forms of duodenal atresia, which occurs in approximately 1 in 1000 births. The webs take the form of an intact membrane seen obstructing the lumen. Incomplete webs may present as the "windsock deformity," in which an incomplete and distensible membrane spanning the lumen stretches and balloons downstream. It is often associated with abnormalities of the biliary system.

As is alluded to above, the diagnosis of duodenal webs is usually made on the first day of life. Plain radiographs will demonstrate the "double-bubble sign" (Fig. 3) of air in the distended stomach and proximal duodenum without visualization of more distal gas. Contrast studies are rarely indicated and may be precluded secondary to the risk of aspiration of the contrast medium. Annular pancreas and malrotation of the bowel with Ladd's bands must be considered in the differential diagnosis. Increasingly, prenatal ultrasound can suggest the diagnosis.

A number of associated conditions are seen in patients with duodenal webs, including polyhydramnios (5–20%), Down's syndrome (20–30%), VACTERAL anomalies, jaundice, esophageal atresia, and congenital heart disease. The initial treatment of the affected infant includes nasogastric tube decompression and correction of electrolyte balance. Associated abnormalities such as those noted above should be excluded before repair, as 33% of these infants have life-threatening abnormalities. Repair by duodenodudenostomy or duodenoplasty can then be undertaken.

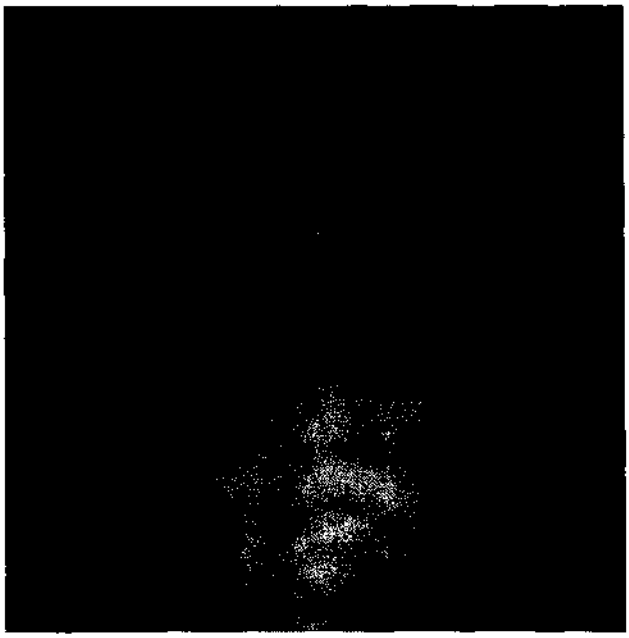

FIGURE 3 The "double-bubble" sign indicative of duodenal obstruction.

### See Also the Following Articles

Esophagus, Development • Gastroesophageal Reflux Disease (GERD) and Congenital Esophageal Obstructive Lesions, Pediatric • Neonatal Tracheoesophageal Anomalies • Pyloric Stenosis

### Further Reading

Anderson, L. S., *et al.* (1973). Cartilaginous esophagus: A cause of esophageal stenosis in infants and children. *Radiology* 108, 66.

Buckley, K., *et al.* (1998). Schatzki's ring in children and young adults: Clinical and radiologic findings. *Pediatr. Radiol* 28, 884–886.

Chen, Y. M., *et al.* (1987). Natural progression of the lower esophageal ring. *Gastrointest. Radiol.* 12, 93–98.

Ekberg, O., and Nylander, G. (1983). Webs and web-like formations in the pharynx and cervical esophagus. *Diag. Imaging* 52, 10–18.

Hirano, I., *et al.* (2000). Clinical and manometric features of the lower esophageal ring. *Am. J. Gastroenterol.* 95, 43–49.

Johnson, M. C. (2001). The esophagus. *Primary Care* 28, 1–20.

Ladd, A. P., and Madura, J. A. (2001). Congenital duodenal anomalies in the adult. *Arch. Surg.* 136, 576–584.

Wong, P. (2002). Esophageal webs and rings. Available at http://www.emedicine.com.

# Whipple's Disease

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*Tropheryma whipplei* The bacterium causing Whipple's disease.

Whipple's disease A rare chronic disease. The main symptoms are weight loss, arthralgia, diarrhea, and abdominal pain. The current medical treatment still depends on empiric antibiotic regimens with variable rates of success.

**Whipple's disease was first described in 1907 as intestinal lipodystrophy. It is a rare infectious disease caused by the actinomycete *Tropheryma whipplei*. Whipple's disease occurs mostly in middle-aged caucasian men. As of 1987, approximately 700 cases have been reported in the literature.**

## ETIOLOGY, CLINICAL FEATURES, AND DIAGNOSIS

*T. whipplei* is probably a ubiquitously occurring bacterial agent as its presence in soil, in waste water, and in the saliva of healthy persons has been ascertained by polymerase chain reaction (PCR). It is an actinomycete that was phylogenetically characterized in 1991 and now has been cultured and formally named. The bacterium has a typical morphology with a trilamellar cell wall as observed by electron microscopy (Fig. 1). *T. whipplei* can be found intra- and extracellularly and infested tissue pathognomonically reveals a strong positivity for polysaccharides, mucoproteins, and glucoproteins in the periodic acid Schiff (PAS) reaction. *T. whipplei* is poorly gram-stained in tissue but is gram-negative in cell culture. Histologically, the frequently affected small intestine often appears thickened and edematous with a marked infiltration by large macrophages and lipid deposits, which are the result of villous lymphatic blockade.

There is evidence that host factors contribute to the clinical manifestations of Whipple's disease. Cellular immune function, i.e., macrophages and T lymphocytes, seem to be primarily affected. In addition to a reduced proliferation rate of T lymphocytes after stimulation, a reduced CD4/CD8 ratio can be found. Other alterations are an increased memory T-cell subpopulation with a simultaneous decrease in naive T cells. A diminished expression of CD11b and a significantly reduced production of $T_H1$ cytokines (interleukin-12 and interferon-γ) after stimulation of monocytes *in vitro* are also seen. The pathogenetic significance of the latter immune defects is underscored by the fact that they are not only present in florid disease but persist even in patients with long-term remission.

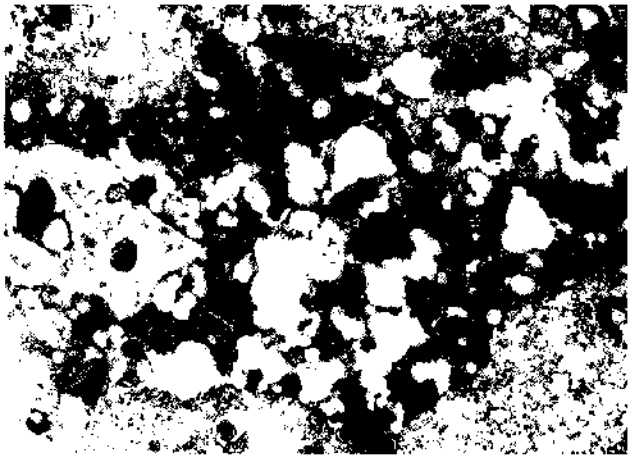

**FIGURE 1** Electron microscopic view of *T. whipplei* (×20,000), showing abundant rod-shaped bacteria with an approximate size of 0.5–1.5 × 2.5 μm.

The main clinical features are weight loss due to abdominal manifestations, fever, or inappetence, as well as nondestructive, migratory, seronegative arthropathies often preceding other symptoms by many years. Abdominal symptoms such as diarrhea and abdominal pain may be accompanied by the full spectrum of a malabsorption syndrome. Therefore, Whipple's disease was considered mainly a gastrointestinal disease for a long time. However, as the bacterium spreads systemically, numerous other organs and systems, such as the heart, lungs, and central nervous system, may be affected (Table I).

The diagnosis is usually made by duodenal biopsy. Diagnosis may also be established, for example, from lymph node biopsies, endocardial tissue, synovia, and

 

TABLE I Clinical Features of Whipple's Disease

| | Approximate incidence (%) |
|---|---|
| **Major clinical features** | |
| Weight loss | 95 |
| Arthropathy | 85 |
| Diarrhea | 75 |
| **Frequent signs and symptoms** | |
| Systemic | |
| Fever | 50 |
| Lymphadenopathy | 50 |
| Hyperpigmentation | 45 |
| Gastrointestinal | |
| Abdominal pain | 65 |
| Occult bleeding | 25 |
| Abdominal mass | 20 |
| Splenomegaly | 15 |
| Hepatomegaly | 15 |
| Ascites | 10 |
| Other | |
| Hypotension | 40 |
| Peripheral edema | 35 |
| Cardiac murmurs | 35 |
| Myalgia | 25 |
| Chronic cough | 20 |
| **Other less frequent clinical signs** | |
| Pleuritis | |
| Pleural effusion | |
| Endocarditis | |
| Muscle wasting | |
| Glossitis | |
| Peripheral neuropathy | |
| Eye involvement (e.g., visual loss, uveitis, retinitis) | |
| CNS involvement (e.g., dementia, ophthalmoplegia, myoclonus, ataxia, nystagmus) | |

cerebrospinal fluid (CSF) and these tests should also be confirmed by duodenal biopsy. The presence of bacterial DNA can be verified using PCR. Bacterial DNA often can be found in the CSF at the time of diagnosis.

## THERAPY

Due to the small number of cases, antibiotic treatment is based on empiric observations and there is still no evidence-based therapy regimen. In the initial therapy, ceftriaxone, which has good CNS penetration, is frequently used at a dose of 2 g/day intravenously for 2 weeks. This should be followed by a long-term oral antibiotic regimen. Most frequently, trimethoprim/sulfamethoxazole (800 mg/160 mg), which has a good penetration of the blood–brain barrier, is used for a >1-year period. In many cases, this therapy is able to eliminate *T. whipplei*, which should be checked histologically after 6 and 12 months. However, in cases with refractory or relapsing disease, or in the case of a CNS manifestation, the prognosis may be poor. Up to 40% of all patients may have a clinical relapse with a higher incidence of neurological symptoms.

### See Also the Following Articles

Diarrhea • Malabsorption

### Further Reading

Dobbins, W. O., III (1987). "Whipple's Disease." Charles C. Thomas, Springfield, IL.

Dutly, F., and Altwegg, M. (2001). Whipple's disease and "*Tropheryma whipplei*." *Clin. Microsc. Rev.* **14**, 561–583.

Fenollar, F., and Raoult, D. (2001). Molecular techniques in Whipple's disease. *Expert Rev. Mol. Diagn.* **1**, 299–309.

Marth, T. (1999). Whipple's disease. *In* "Principles and Practice of Infectious Disease" (G. L. Mandell, J. E. Bennett and R. Dolin, eds.), 5th Ed., pp. 1170–1174. Churchill Livingstone, Philadelphia, PA.

Marth, T., and Raoult, D. (2003). Whipple's disease. *Lancet* **36**, 239–246.

# Wilson's Disease

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**ATP7B** Human copper-transporting ATPase that is the product of the Wilson's disease gene (*ATP7B*). The gene is expressed mainly in hepatocytes; the encoded protein maintains copper homeostasis by exporting copper from the hepatocyte into bile.

**ceruloplasmin** Copper-containing serum glycoprotein produced mainly in the liver; binds six copper atoms per molecule of protein.

**Kayser–Fleischer ring** Corneal deposits of copper present in Descemet's membrane; visible on slit lamp examination, and, when more pronounced, by direct visualization.

**In Wilson's disease, copper accumulates to toxic levels in the liver, brain, and other sites in the body. When discovered in a timely fashion, many of the toxic effects of copper accumulation can be prevented or reversed by medical therapy, which must be continued for life. Failure to initiate treatment, or interruption of treatment, can lead to liver injury and liver failure and death, or to neurological and psychiatric signs and symptoms. In some patients with fulminant liver failure due to Wilson's disease, or in patients with advanced liver disease that fails to respond to medical treatment, liver transplantation can be lifesaving and curative.**

## INTRODUCTION

Wilson's disease is present in all populations, with an incidence of ~1/30,000 individuals. The gene for Wilson's disease, *ATP7B*, encodes a copper-transporting ATPase that resides mainly within hepatocytes.

## PATHOPHSYIOLOGY

Wilson's disease (WD) is an autosomal recessive disorder in which copper accumulates to toxic levels in the liver and subsequently in the neurologic system and other tissues. The gene for WD, *ATP7B*, is located on chromosome 13 and encodes a copper-transporting ATPase expressed mainly in hepatocytes. Individuals homozygous for a single *ATP7B* mutation, or more commonly with two different mutations of this gene (compound heterozygotes), have reduced or failed copper transport activity of the ATP7B protein. Loss of this physiologic copper transport function reduces biliary copper excretion; this is responsible for hepatic copper accumulation and leads to a reduced copper incorporation into ceruloplasmin and thereby to decreased levels of the ATP7B protein in the circulation of most patients, due to the instability of the protein without copper. Tissue accumulation of copper results in cellular injury by oxidative damage to membranes, organelles such as mitochondria, and DNA, and to altered protein synthesis, among other effects. Liver injury manifests as mild steatosis and inflammation early on, and to chronic injury, fibrosis, cirrhosis, and liver failure. Excess copper appears in the circulation following hepatic copper accumulation and eventually toxic accumulation in the central nervous system with resultant neurologic or psychiatric manifestations. Other organs that may be affected by toxic copper accumulation include the kidneys, heart, and bone.

## DIAGNOSIS

The clinical presentation of Wilson's disease varies widely, but mainly presents as hepatic or neurologic disease. Liver disease typically presents within the first two decades of life, and later on, typically in the third decade, neurologic or psychiatric signs and symptoms may be evident. Patients with liver disease may be asymptomatic or they may experience symptoms of chronic liver disease such as fatigue or jaundice, or may manifest signs or symptoms of portal hypertension such as ascites and varices without or with bleeding. Some patients may have chronic hepatitis with features indistinguishable from autoimmune hepatitis. In about 5% of cases, the sudden onset of jaundice or ascites with associated hemolysis heralds the onset of acute fulminant hepatic failure.

Neurologic manifestations of WD are mainly due to injury to the basal ganglia, but many different parts of the brain may be affected. Symptoms may include diminished motor coordination, tremor with deteriorating handwriting and micrographia, drooling, dysarthria, dystonia, and spasticity. Transfer dysphagia with

 

the risk of aspiration may occur in some patients. Psychiatric ailments range from behavioral changes and anxiety disorders to depression or even psychosis.

WD must be considered in any patient below the age of 45 years with unexplained liver disease or cirrhosis, and in patients with neurologic and psychiatric symptoms and evidence of liver disease. Individuals with hepatic histology suspicious for WD, pediatric patients with autoimmune features not responsive to steroids and lacking typical markers, patients with brain imaging demonstrating compatible findings, and patients in whom Kayser--Fleischer rings are identified should be evaluated for WD.

The diagnosis of WD is established by a combination of clinical signs and biochemical studies or by molecular methods (see Table I). Clinical findings that include Kayser--Fleischer (KF) rings and corneal deposits of copper in Descemet's membrane are pathognomonic and are present in almost all patients with WD with neuropsychiatric manifestations; these symptoms are best detected by slit lamp examination. However, KF rings may be present in only ~50% of patients presenting with liver disease, and may rarely be found in patients with chronic cholestasis such as primary biliary cirrhosis or primary sclerosing cholangitis. Sunflower cataracts are another rare ocular finding associated with WD, and lunulae cerulae (blue lunules) are another dermatologic abnormality present very rarely in patients with WD. Other nondiagnostic findings include evidence of stigmata of chronic liver disease and cirrhosis and Parkinsonian features on neurological examination.

Reduced levels of serum ceruloplasmin (typically <20 mg/dl) are present in ~95% of patients with WD, but also in 20% of heterozygous carriers without manifestations of WD. Ceruloplasmin levels in the circulation may also be reduced in patients with severe hepatic insufficiency, in protein-losing enteropathy or

**TABLE I Diagnostic Testing for Wilson's Disease**

| Test | Results |
|---|---|
| Ophthalmologic slit lamp examination | Kayser–Fleischer rings and sunflower cataracts are absent in normal individuals; Kayser–Fleischer rings absent early on in patients with WD; present in only 50% of patients with hepatic presentation; found in 98% of patients with neurologic signs or symptoms; sunflower cataracts may also be seen on slit lamp exam in patients with WD; Kayser--Fleischer rings and sunflower cataracts abate with treatment for WD |
| Serum ceruloplasmin | Normal 20–40 mg/dl, elevated with acute phase and in pregnancy and with use of estrogens; less than 20 mg/dl in 95% of patients and 20% of heterozygous carriers; physiologically decreased in newborns, undetectable in rare patients with aceruloplasminemia; below 20 mg/dl with severe hepatic insufficiency and in severe protein-loss states |
| Serum copper | Normally ~100 μg/dl, decreased in most patients, typically <80 μg/dl; proportion not bound to ceruloplasmin >10% in patients and total serum copper and markedly elevated above 200 μg/dl in fulminant hepatitis due to Wilson's disease |
| 24-Hour urinary copper | Normal <50 μg/24 h, greater than 100 μg/24 h in most symptomatic patients and following chelation treatment; postpenicillamine (500 mg given twice, 12 h apart) >1600 μg in untreated patients |
| Hepatic copper concentration | Normal <40 μg/g dry wt liver; greater than 250 μg/g dry wt liver in patients; may be increased in other cholestatic disorders, idiopathic copper toxicosis |
| Hepatic histology | Abnormal findings in patients include steatosis, glycogen nuclei, fibrosis, chronic active hepatitis and cirrhosis; marked degeneration of hepatocytes, pleiocytosis, and nuclear irregularities in fulminant hepatitis |
| Electron microscopy for hepatic ultrastructure | Abnormal in untreated patients; dilatation of mitochondrial cristae and crystalline deposits (present when steatosis is seen on light microscopy); dense lysosomes later on |
| Histochemistry for copper | Absent normally; in some patients, positive staining is present in some but not all liver nodules; absent staining does not exclude Wilson's disease |
| Radiological imaging of the brain: MR or CT imaging | Normal in the absence of Wilson's disease and in many patients early on; findings in patients with neurologic or psychiatric symptoms include atrophy and alterations in basal ganglia, subcortical white matter, midbrain, and pons; abnormalities can be present in some asymptomatic patients |
| Molecular diagnostic studies: haplotype analysis and mutation analysis | Haplotype: same as proband in patients, different in carriers and unaffected siblings; mutations: patients have disease-specific mutations on each allele; most useful in populations with dominant mutations |

nephropathy, and in the rare genetic disorders Menke's disease and aceruloplasminemia. Serum copper not bound to ceruloplasmin is increased in untreated patients, but total serum copper is typically reduced because ~90% is bound to ceruloplasmin, which is reduced in the vast majority of patients. Urinary copper excretion is increased to >100 μg for 24 hours in most untreated patients with symptomatic disease. Low serum uric acid levels are found in many patients, and aminoaciduria and electrolyte changes due to renal tubular acidosis may be present.

Liver biopsy still plays an important role in the diagnosis of WD. Copper quantitation from the biopsy specimen is a critical test and reveals a level above 250 μg/g dry weight in almost all untreated patients. Characteristic histologic features of the earlier stages of the disorder include steatosis, microvesicular and macrovesicular fatty changes, with glycogenated nuclei in some hepatocytes. Varying degrees of fibrosis and inflammatory infiltrate can be found. Cirrhosis is present in most patients by the time they present with hepatic insufficiency or with neurological disease. Histochemical staining of liver biopsy specimens for copper typically reveals positive areas in some nodules, with absence in others. The absence of histochemically identifiable copper does not exclude WD. Ultrastructural analysis of liver specimens at the time steatosis is present reveals specific mitochondrial abnormalities that include dilated cristae and crystalline inclusions. For patients presenting with neurological or psychiatric disease, common abnormalities present on brain imaging that should suggest a diagnosis of WD include increased density of the basal ganglia on computer tomography (CT) or hyperintensity of this region on T2 magnetic resonance (MR) imaging. Abnormal findings are not limited to the basal ganglia, and other abnormalities have been described, including regions of the pons, white matter, and cerebellum.

The diagnosis of WD is established by the presence of KF rings and a decreased level of serum ceruloplasmin, of KF rings and neurologic or psychiatric symptoms, and of elevated hepatic copper levels with appropriate histology. Haplotype or polymorphism analysis can be used to identify affected siblings or offspring; however, the diagnosis must be firmly identified in the proband. Direct identification of *ATP7B* mutations is possible but is limited by the size of the gene and the large numbers of mutations associated with the WD phenotype, and the limited availability of testing.

Patients with fulminant hepatic failure due to WD have markedly elevated serum copper concentration and urinary copper excretion, and most have a lowered serum ceruloplasmin. Kayser–Fleischer rings may be present in about 50% of patients. These patients invariably have cirrhosis underlying the acute liver injury, which likely accounts for the relatively low levels of transaminase elevations despite the massive hepatic injury. Unique to acute fulminant liver failure due to WD is a relatively low alkaline phosphatase level, with the ratio of alkaline phosphatase (units/liter) to bilirubin (milligrams/deciliter) of ≤2.0. Hepatic copper is almost always elevated above 250 μg/g dry weight in these individuals despite the massive hepatic necrosis and presence of cirrhosis.

## TREATMENT

Treatment options for WD include lifelong medical therapy with oral chelating agents or zinc (see Table II), and liver transplantation. Dietary restrictions of copper intake are recommended along with medical therapy. The chelating agents penicillamine and trientine promote renal copper excretion and are recommended as first-line therapy for symptomatic patients with hepatic or neurologic disease, and, at lower dosages, these agents may be used for maintenance therapy. Zinc acts to block copper absorption from the gut at the level of the enterocyte, and is mainly used for maintenance therapy or initial therapy of asymptomatic patients. Liver transplantation restores a normal phenotype with respect to copper metabolism, and no further therapy specific for Wilson's disease is required.

Initial treatment with penicillamine consists of dosages that are increased to 1–2 g/day over a few weeks, and 750–1000 mg/day is used for maintenance therapy. Some patients with WD with neurologic symptoms initially treated with this drug have worsening neurologic disease that may become irreversible. Early side effects include hypersensitivity reactions, and nephrosis or a lupuslike syndrome with associated hematuria, proteinuria, and positive antinuclear antibodies will occur later on. Late reactions include dermatologic side effects such as progeric skin changes, elastosis perforans serpingosa, pemphigous or pemphigoid lesions, lichen planus, and apthous stomatitis, and rarely systemic anaphylaxis, myasthenia gravis, polymyositis, dysgeusia and loss of taste, IgA depression, and serous retinitis. An adverse drug reaction to penicillamine should prompt its discontinuation and a change to an alternative treatment. Monitoring of therapy includes clinical examination and biochemical determination of non-ceruloplasmin-bound copper (derived from subtracting the amount of ceruloplasmin-bound copper from the total serum copper),

TABLE II Treatment Options for Wilson's Disease

| Medication | Mode of action | Dosages (total/24 h) | Adverse effects |
|---|---|---|---|
| *d*-Penicillamine (Cuprimine) | Chelating agent, induces cupriuresis | 750–2000 mg in two to three divided doses apart from meals; maintenance 750–1000 mg; requires supplemental pyridoxine | Worsening with initial treatment of neurlogic symptoms in 10–50% of cases; initial hypersensitivity reactions; marrow suppression; lupuslike syndrome; nephrosis; dermatologic toxicity; rare Goodpastures syndrome |
| Trientine (Syprine) | Chelating agent, induces cupriuresis | 750–1500 mg in two to three divided doses apart from meals; maintenance, 750–1000 mg | Lupuslike syndrome; nephrosis; marrow suppression |
| Zinc (Galzin) | Blocks intestinal uptake of copper by enterocytes | 100–150 mg in two to three divided doses apart from meals | Gastric irritation |

blood counts, liver functions testing, and urinalysis to look for the appearance of cellular elements or protein. Urinary copper excretion over 24 hours is usually greater than 1 mg/day during initial treatment and afterward is typically reduced to between 250 and 500 μg/day, but is dosage dependent.

Trientine, developed for treating penicillamine-intolerant patients, may be used as first-line therapy when administered in two to four divided dosages totaling up to 1500 mg/day, and as maintenance therapy with a reduced dosage of 750–1000 mg/day. Trientine has a better safety profile compared to penicillamine, with only extremely rare reports of hypersensitivity reactions. Known toxicity includes bone marrow suppression, sideroblastic anemia (the result of an induced copper deficiency), and lupuslike reactions. Monitoring of therapy is the same as for penicillamine.

Zinc, used mainly as a maintenance therapy and for the initial therapy of asymptomatic patients, is administered in three daily dosages of 50 mg (of elemental zinc) for adults and 25 mg for children. This dosage effectively achieves a negative copper balance in most individuals. The most important side effect of zinc affecting a minority of patients is gastric upset, and this may be related to the particular zinc salt used. Monitoring of zinc therapy includes determination of non-ceruloplasmin-bound copper and 24-hour urinary copper excretion, the latter being below 100 μg/day in effectively treated patients.

Tetrathiomolybdate is a potent copper chelator that remains currently under investigation for the initial treatment of neurologic WD in the United States. Reversible side effects of tetrathiomolybdate therapy include anemia and neutropenia. Further recommendations regarding this drug await the completion of ongoing clinical trials.

Patients with fulminant hepatic failure due to WD and those in whom medical therapy is ineffective or is interrupted by resulting liver failure require liver transplantation for survival. Following the onset of fulminant liver failure in WD, there is a large release of copper into the circulation that contributes renal tubular injury and reduced kidney function. Plasma exchange, plasmapheresis, and other forms of dialysis, including albumin dialysis, are useful to help rapidly lower copper levels in the circulation and to limit hemolysis and further renal damage, but have not eliminated the need for transplantation of these individuals.

Treatment for WD must continue throughout pregnancy. There are recorded successful pregnancies with administration of penicillamine, trientine, and zinc. No dosage reduction is needed for zinc therapy, whereas the smallest effective dosage of penicillamine or trientine should be administered during pregnancy and until wound healing occurs. Similarly for patients undergoing elective surgical procedures, dosages of chelating agents should be minimized until wound healing is achieved.

## PROGNOSIS

Medical treatment of asymptomatic patients prevents the development of liver or neurological disease. The long-term survival of patients with WD with medical therapy is excellent, even when chronic liver disease and cirrhosis are present at the outset. Patients with cirrhosis still may manifest signs or symptoms due to portal hypertension, including esophageal or gastric varices or ascites. In some patients, neurologic symptoms may

improve with therapy, whereas other patients may worsen during the initial phase of treatment or may develop neurological disease no longer responsive to therapy aimed at WD.

Liver transplant also offers excellent survival, approaching 90% for patients with acute liver failure due to WD, well above the survival of ~60% for all others transplanted for fulminant liver failure. Patients with WD surviving beyond 1 year posttransplant typically have excellent long-term survival.

## See Also the Following Articles

**Ascites • Cirrhosis • Liver Biopsy • Liver Disease, Pregnancy and • Liver Transplantation • Portal Hypertension and Esophageal Varices • Trace Minerals: Metabolism and Deficiency** (Zinc, Copper, Selenium, Manganese)

## Further Reading

Brewer, G. J., Dick, R. D., Johnson, V. D., Brunberg, J. A., Kluin, K. J., and Fink, J. K. (1998). Treatment of Wilson's disease with zinc. XV. Long-term follow-up studies. *J. Lab. Clin. Med.* 132, 264–278.

Brewer, G. J., Dick, R. D., Johnson, V. D., Fink, J. K., Kluin, K. J., and Daniels, S. (2001). Treatment of Wilson's disease with zinc. XVI. Treatment during the pediatric years. *J. Lab. Clin. Med.* 137, 191–198.

Brewer, G. J., Johnson, V. D., Dick, R. D., Hedera, P., Fink, J. K., and Kluin, K. J. (2000). Treatment of Wilson's disease with zinc. XVII. Treatment during pregnancy. *Hepatology* 31, 364–370.

Emre, S., Atillasoy, E. O., Ozdemir, S., Schilsky, M. L., Rathna Varma, C. V. R., Thung, S. N., *et al.* (2001). Orthotopic liver transplantation for Wilson's disease: A single center experience. *Liver Transpl.* 72, 1232–1236.

Martins da Costa, C., Baldwin, D., Portmann, B., Lolin, Y., Mowat, A. P., and Michl-Vergani, G. (1992). Value of urinary copper excretion after penicillamine challenge in the diagnosis of Wilson's disease. *Hepatology* 15, 609–615.

Scheinberg, I. H., and Sternlieb, I. (1984). "Wilson's Disease." W. B. Saunders Co., Philadelphia.

Schilsky, M. L., Scheinberg, I. H., and Sternlieb, I. (1994). Hepatic transplantation for Wilson's disease: Indication and outcome. *Hepatology* 19, 583–587.

Steindl, P., Ferenci, P., Dienes, H. P., Grimm, G., Pabinger, I., Madl, C., *et al.* (1997). Wilson's disease in patients presenting with liver disease: A diagnostic challenge. *Gastroenterology* **113**, 212–218.

Sternlieb, I. (2000). Wilson's disease and pregnancy. *Hepatology* 31, 531–532.

# Xerostomia

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**dysgeusia** Difficulty in tasting.
**dysphagia** Difficulty in swallowing.
**halitosis** Subjective complaint of bad breath.
**salivary hypofunction** Objective diminution of salivary output.
**xerostomia** Subjective complaint of a dry mouth.

**Xerostomia is the subjective complaint of a dry mouth due to salivary hypofunction. Saliva provides host protection, assists in the initiation of food and fluid intake, and enables communication through speech. Without adequate salivary output, oral and pharyngeal health declines as does a person's quality of life. Xerostomia becomes more common with aging and is caused by numerous intraoral and systemic factors.**

## ROLE OF SALIVA IN ORAL AND SYSTEMIC HEALTH

The adequate secretion of saliva is critical for preserving the health of the oral cavity and gastrointestinal system. It provides a physical barrier against irritants, lubricates oral mucosal tissues, aids in the digestion of fats and carbohydrates, and assists with mastication, deglutition, taste, and retention of dentures. Saliva maintains a stable pH in the mouth and esophagus and helps prevent tooth decay and remineralize the dental hard tissues. Saliva contains antibacterial, antiviral, and antifungal factors that help maintain the oral commensal flora.

## ORAL AND SYSTEMIC EFFECTS OF SALIVARY HYPOFUNCTION

Salivary function is age-stable in healthy adults, yet xerostomia is more common in the elderly due to oral and systemic factors that cause salivary hypofunction. Inadequate output causes persistent complaints of xerostomia and halitosis and leads to multiple oral problems: new and recurrent dental caries, mucositis, pain, and increased susceptibility to microbial infections. The most prevalent infection is caused by *Candida albicans*, observed as angular cheilitis of the lips, erythematous candidiasis (denture stomatitis), and pseudomembraneous candidiasis. Salivary hypofunction also causes problems with chewing and wearing dentures, dysphagia, and dysgeusia, resulting in altered food and fluid selection, compromising nutrition.

## INTRAORAL SOURCES OF SALIVARY PATHOLOGY

Bacterial infections (e.g., parotitis) occur secondary to salivary hypofunction. Colonization and infection (e.g., *Staphylococcus aureus*, *Staphylococcus pyogenes*, *Streptococcus pneumonia*, *Escherichia coli*) occur following obstruction of a duct, causing swelling, purulence, and pain. Viral infections preferentially involve parotid glands: paramyxovirus (mumps) and cytomegalovirus infections affect young and immunocompromised adults. Obstructions of excretory ducts are caused by trauma in the lips (mucocele of a minor gland) and floor of the mouth (ranula of the sublingual or submandibular gland) or by calcification of mucous plugs in major glands (sialoliths, stones).

Most salivary tumors are benign, the most common being pleomorphic adenoma of the parotid gland, which presents as an asymptomatic mass in the tail of the gland. Malignant tumor incidence increases with age; they are most prevalent in the palatal minor glands and the submandibular and sublingual glands. Mucoepidermoid carcinoma is the most common malignant salivary gland tumor, followed by adenoid cystic carcinoma, acinic cell carcinoma, and adenocarcinoma. Presentation includes a swelling with nerve paralysis, pain, or facial paresis.

## EXOGENOUS AND SYSTEMIC SOURCES OF SALIVARY PATHOLOGY

Medications are the most likely cause of salivary hypofunction, particularly those with anticholinergic effects (e.g., antidepressants, sedatives, tranquilizers, antihistamines, cytotoxic agents, antihypertensives, anti-Parkinson's disease drugs, and anti-spasmodic/anti-seizure drugs). Chemotherapy can cause acute

 

yet reversible changes in salivary function and radioactive iodine ($^{131}$I) causes parotid but not submandibular dysfunction. Head and neck radiotherapy, used for cancer, is the prime exogenous source of salivary hypofunction. Radiotherapy-induced xerostomia is usually irreversible and permanent, causing a lifetime of oral–pharyngeal disorders.

Sjögren's syndrome, an autoimmune exocrinopathy, is the most common disorder causing salivary hypofunction. It is characterized by progressive and irreversible xerostomia and xerophthalmia (dry eyes). Other autoimmune diseases with salivary hypofunction include rheumatoid arthritis, scleroderma, and systemic lupus erythematosus. Human immunodeficiency virus infection, diabetes, Alzheimer's disease, Parkinson's disease, strokes, and cystic fibrosis are also associated with salivary hypofunction.

## TREATMENT OF SALIVARY HYPOFUNCTION

Appropriate diagnosis is required before initiation of therapy. To prevent the development of xerostomia-induced oral sequelae, frequent dental evaluations are required, as is oral hygiene after each meal and before bedtime with fluoridated dentifrices, gels, and rinses to avoid dental caries. Regular hydration with water, not sugared beverages, is helpful. Sugar-free chewing gum, candies, and mints can stimulate remaining salivary secretions, whereas artificial saliva and lubricants may assist when there is no remaining salivary tissue. Counseling regarding a well-balanced nutritionally adequate diet should be provided. Dysphagia can be improved with oral moisturizers, lubricants, and careful use of fluids during eating. Candidiasis responds to topical antifungal agents (e.g., clotrimazole, nystatin) and appropriate denture hygiene, and parotitis is treated with broad-spectrum antibiotics (e.g., Augmentin).

Salivary lesions and tumors must undergo histopathological evaluation and imaging (sialograms, radiographs, radioactive isotype scintiscans, magnetic resonance imaging, and computed tomography scans). Most tumors are treated with excision and possibly radiotherapy. Drug-induced xerostomia requires assessment of all medications, with attempts to eliminate, diminish, or substitute medications causing hypofunction. Secretagogues are available (pilocarpine 5 mg tid and qhs; cevimeline 30 mg tid) to increase secretions and diminish xerostomia in patients with remaining exocrine tissue.

## See Also the Following Articles

**Candidiasis • Dysphagia • Halitosis • Salivary Glands, Physiology • Sjögrens Syndrome**

## Further Reading

Atkinson, J. C., and Wu, A. (1994). Salivary gland dysfunction: Causes, symptoms, treatment. *J. Am. Dent. Assoc.* **125**, 409–416.

Fox, P. C. (1997). Management of dry mouth. *Dent. Clin. N. Am.* **41**, 863–876.

Fox, R. I., Stern, M., and Michelson, P. (2000). Update in Sjögren syndrome. *Curr. Opin. Rheumatol.* **12**, 391–398.

Narhi, T. O., Meurman, J. H., and Ainamo, A. (1999). Xerostomia and hyposalivation: Causes, consequences and treatment in the elderly. *Drugs Aging* **15**, 103–116.

Silverman, S., Jr. (1999). Oral cancer: Complications of therapy. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endo.* **88**, 122–126.

Sreebny, L. M., and Schwartz, S. S. (1997). A reference guide to drugs and dry mouth. 2nd Ed. *Gerodontology* **14**, 33–47.

# *Yersinia*

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**adenitis** Glandular inflammation.
**bacteriophage typing** Bacterial typing that differentiates between bacteria or strains of bacteria by their susceptibility to one or more bacteriophages.
**erythema nodosum** Disorder characterized by tender red bumps, usually found on the front of the lower leg.
**ileitis** Inflammation of the ileum.
**Reiter's syndrome** Chronic form of inflammatory arthritis characterized by the inflammation of the joints, the eyes, and the genital, urinary, or gastrointestinal system.

**The genus *Yersinia* is composed of 10 species of gram-negative bacilli, of which three, *Yersinia pestis* (plague bacillus), *Yersinia enterocolitica*, and *Yersinia pseudotuberculosis*, are well-recognized human pathogens. Whereas isolates of *Y. pestis* and *Y. pseudotuberculosis* are inherently pathogenic, virulence among *Y. enterocolitica* isolates differs by biogroup and serogroup.**

## MICROBIOLOGY

Many of the identifying characteristics and virulence factors of *Yersinia enterocolitica* are influenced by growth temperature. For instance, *Y. enterocolitica* is nonmotile at 37°C but is motile at 25°C; plasmid-encoded virulence factors are expressed at 37°C and are repressed or absent at 25°C. Therefore, full characterization of an isolate as *Y. enterocolitica* should include tests determined at two incubation temperatures. *Yersinia enterocolitica* grows on routine bacteriologic media used for the isolation of other enteric bacteria. On these media, however, because *Y. enterocolitica* produces only pinpoint colonies after 24 hours of incubation, colonies may be overlooked in stool cultures containing a multiplicity of bacterial species. The use of cefsulodin–irgasan–novobiocin (CIN) agar enhances recovery; *Y. enterocolitica* produces red colonies on this medium.

Culture of stools of patients with acute gastroenteritis due to pathogenic *Y. enterocolitica* serogroups (O3, O5,27, O8, O9) produces numerous colonies on routine isolation media. However, in those instances when *Y. enterocolitica* is sought during convalescence from acute enteritis, or for surveillance during an outbreak, cold (4°C) enrichment of stool specimens in phosphate-buffered saline for up to 4 weeks with periodic subculture may enhance recovery. *Yersinia enterocolitica* isolates recovered after prolonged cold enrichment should be biogrouped and serogrouped before clinical significance is ascribed to the isolate. In many instances, such isolates have an environmental origin (biogroup 1A) and lack virulence attributes.

*Yersinia enterocolitica* biogrouping schemas delineate six biogroups that correlate with ecologic distribution, serogroup designation, and human pathogenic potential. In the United States, biogroup 4, serogroup O3 is the most frequently isolated bio/serogroup, exceeding serogroup O8. Using antisomatic O antisera, *Y. enterocolitica* isolates may be serologically grouped into approximately 60 serogroups. Bacteriophage typing of an isolate also correlates biogroups and serogroups to secondary autoimmune sequelae and epidemiologic distribution.

## EPIDEMIOLOGY

*Yersinia enterocolitica* is widely distributed in terrestrial and freshwater ecosystems and has been recovered from the intestinal tract of numerous mammalian species. *Yersinia enterocolitica* infections have been documented almost globally. Whereas a cooler seasonal prevalence has been recognized in European countries, such a correlation has not been found in the United States or other countries. The frequency of infection seems to correlate with the porcine reservoir of pathogenic serogroups (O3, O5,27, O8, O9) and consumption of undercooked or raw pork products, or their preparation.

Although most sporadic infections with *Y. enterocolitica* cannot be traced to a specific exposure, ingestion of contaminated milk or other foods, contact with sick animals or perhaps index cases, and transfusion of contaminated blood are also routes of transmission and acquisition.

 

## PATHOGENESIS

Gastrointestinal disease is the most common clinical manifestation of *Y. enterocolitica* infection. Once ingested, *Y. enterocolitica*, aided by its motility, traverses the intestinal lumen and binds to and penetrates M cells, to invade underlying Peyer's patches of the distal ileum; this results in the formation of microabscesses, ulceration of the overlying epithelium, and an inflammatory reaction. Spread to the mesenteric lymph nodes may lead to abscesses in the medullary region and pain in the lower quadrant, mimicking appendicitis. Extensive ulceration of the intestinal tract and death have occurred in the course of *Y. enterocolitica* serogroup O8 infection. Acute enteritis with inflammatory cells and occasionally bloody, watery stools characterize infection in children. Concomitant *Y. enterocolitica* bacteremia may be present in infants with enteritis. In young adults, acute terminal ileitis and mesenteric adenitis are the more common presentations.

*Yersinia enterocolitica* extraintestinal disease depends on host immune status and the pathogenic potential of the infecting strain. A striking characteristic of *Y. enterocolitica* bacteremia is the increased incidence in people with iron overload diseases or in those being administered iron chelating agents. Secondary manifestations of bacteremia may involve every organ of the body, including the endovasculature and the central nervous system, and may even lead to cutaneous lesions.

Bacteremia with *Y. enterocolitica* may also occur by transfusion of contaminated blood. After the first report in 1975, 36 cases of *Y. enterocolitica* transfusion associated-bacteremia were documented up to 1996. These cases were predominantly associated with transfusion of packed red blood cells, including autologous transfusions. Shock, with and without disseminated intravascular coagulation, occurred in all 36 recipients, and death occurred in 19 patients. The source of *Y. enterocolitica* contamination was asymptomatic bacteremia in the donor.

Secondary immunologically mediated nonsuppurative sequelae of *Y. enterocolitica* infection include polyarticular arthritis and erythema nodosum (most common) and Reiter's syndrome, reported mainly among northern Europeans. Most patients manifesting postyersinial reactive arthritis are HLA-B27 positive.

## VIRULENCE FACTORS

Human pathogenic strains of *Y. enterocolitica* possess plasmid- and chromosomal-encoded virulence determinants. Those specified by a 70- to 75-kb plasmid are expressed mainly at 37°C and confer resistance to phagocytosis and intracellular killing by macrophages. Chromosomally encoded determinants include an outer membrane protein named invasin, maximally produced at 25°C, which binds to host cells through β1 integrins, aiding initial colonization. Adaptation to 37°C triggers the plasmid-encoded virulence attributes and another chromosomally encoded outer membrane attachment/invasion locus (Ail) protein. Presence of the gene for Ail also allows *Yersinia* to resist serum bactericidal activity. *Yersinia enterocolitica* produces a heat-stable enterotoxin but its role in diarrheal disease is disputed because it is maximally produced below 30°C in late log-phase broth cultures.

## TREATMENT

*Yersinia enterocolitica* is susceptible *in vitro* to trimethoprim-sulfamethoxazole (TMP-SMX), third-generation cephalosporins, aminoglycosides, imipenem, aztreonam, and quinolones. There is a trend of increasing resistance to TMP-SMX and chloramphenicol in Spain. Because the mean duration of symptoms in children is 14 days, controversy exists over the need to treat uncomplicated *Y. enterocolitica* enteritis. Extraintestinal infection, such as bacteremia in infants with enteritis, in immunocompromised hosts, or in people with iron overload merits antiyersinial therapy.

### See Also the Following Articles

**Foodborne Diseases • Food Poisoning • Food Safety • *Salmonella***

### Further Reading


Bliska, J. B., and Falkow, S. (1992). Bacterial resistance to complement killing mediated by the Ail protein of *Yersinia enterocolitica*. *Proc. Natl. Acad. Sci. U.S.A.* **89**, 3561–3565.

Bottone, E. J. (1997). *Yersinia enterocolitica*: The charisma continues. *Clin. Microbiol. Rev.* **10**, 257–276.

Bottone, E. J. (1977). *Yersinia enterocolitica*: A panoramic view of a charismatic microorganism. *Crit. Rev. Microbiol.* **5**, 211–241.

Cover, T. L., and Aber, R. C. (1989). *Yersinia enterocolitica*. *N. Engl. J. Med.* **321**, 16–24.

Lee, L. A., Gerber, A. R., Lonsway, D. R., *et al.* (1990). *Yersinia enterocolitica* infections in infants and children associated with the household preparation of chitterlings. *N. Engl. J. Med.* **322**, 984–987.

Tauxe, R. V., Vandepitte, J., Wauters, G., *et al.* (1987). *Yersinia enterocolitica* infections and pork: The missing link. *Lancet* **1**, 1129–1132.

Van Noyen, R., Vandepitte, J., and Wauters, G. (1980). Nonvalue of cold enrichment of stools for isolation of *Yersinia enterocolitica* serotype 3 and 9 from patients. *J. Clin. Microbiol.* **11**, 127–131.

# Zenker's Diverticulum

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**Zenker's diverticulum** Outpouching in the posterior pharyngeal wall immediately above the upper esophageal sphincter.

**A diverticulum is a sac that protrudes from the wall of the gastrointestinal tract. A true diverticulum contains all layers of the gastrointestinal wall. Most diverticula are false diverticula, consisting of mucosa, submucosa, and a few muscle fibers.**

## INTRODUCTION

Zenker's diverticulum, also called pharyngoesophageal diverticulum, is described as an esophageal pouch. In fact, this type of diverticulum occurs in the pharynx, above the upper esophageal sphincter (UES), and should be considered a hypopharyngeal diverticulum. Pharyngoesophageal diverticulum was first described by Ludlow in 1769. In 1877, Zenker and von Ziemssen, in a compilation of five cases of their own together with 22 previously reported cases, clarified the then uncertain nature of a disease defined earlier by Ludlow as a "preternatural dilatation of, and bag formed in, the pharynx." Subsequently, this condition was given Zenker's name.

Esophageal diverticula are rare, occurring in less than 1% of upper gastrointestinal X rays and accounting for less than 5% of cases of dysphagia. The prevalence of Zenker's diverticulum has been reported to range between 0.01 and 0.11%. The prevalence is higher in the elderly, predominantly in women, in whom the occurrence of Zenker's diverticulum increases to about 50% after the age of 70. Zenker's diverticulum grows slowly but continuously. Even if it may be initially totally asymptomatic, with growth it can manifest at a later stage.

## ANATOMY

The pharyngeal constrictor muscles form a funnel, and the mouth of the esophagus is like a transverse slit at the bottom of this funnel. At the esophageal inlet, the fibers of the cricopharyngeal muscle run transversely, thus forming the UES. Above the cricopharyngeal muscle, the walls of the hypopharynx contain the oblique fibers of the inferior constrictor muscles. Between the transverse fibers of the cricopharyngeal below and the oblique fibers of the inferior constrictors above, a triangular area contains fewer muscle fibers and constitutes a region of relative weakness; this is called the triangle of Killian, or Killian's dehiscence. The mucosa of the hypopharynx is allowed to bulge posteriorly at Killian's triangle, and with time, a pouch may develop, forming a Zenker's diverticulum.

## ETIOLOGY AND PATHOPHYSIOLOGY

There is general agreement on the location of Zenker's diverticulum, but several pathogenic mechanisms have been offered, yet none of them has been definitely proved. Age has been considered an important factor. A decrease in tissue elasticity leading to an increased weakness of the triangle of Killian may explain why Zenker's diverticulum is rarely seen before 40 years of age.

The most widely accepted mechanism for the development of a Zenker's diverticulum is a functional disturbance during swallowing in the pressure relationships between the hypopharynx and the UES. Popular hypotheses have included increased resting pressure of the sphincter, lack of complete UES relaxation, and incoordination between hypopharyngeal contraction and sphincter relaxation. At present, poor UES compliance due to a restrictive myopathy rather than cricopharyngeal incoordination appears to account for the genesis of Zenker's diverticulum. The consistent finding in recent studies is increased intrabolus pressure preceding the pharyngeal contraction during swallowing.

## DIAGNOSIS

Symptoms of Zenker's diverticulum depend on the stage of the disease. The frequency and severity of symptoms increase as the disease advances. Clinically, Zenker's diverticulum presents, in order of frequency, with

 

oropharyngeal dysphagia (in up to 98% of cases), regurgitation of undigested food, aspiration, noisy deglutition, halitosis, and changes in the voice. A sensation of sticking in the throat or of vague irritation can be present in the early stages. With time, patients often learn special maneuvers to empty the pouch by pressing on the neck or coughing and clearing the throat. Rarely does the pouch become so large as to obstruct the esophagus.

The most potentially dangerous complications are aspiration, pneumonia (occurring in about 30% of cases), and perforation. Massive bleeding in the diverticulum has been reported. Obstruction and fistula between the diverticulum and the trachea are rare. Carcinoma is an unlikely complication, arising in about 0.4% of cases.

Definitive diagnosis of Zenker's diverticulum is usually accomplished by contrast radiographic examination of the pharynx. Barium swallow with particular attention to the oropharyngeal area is the most helpful procedure, particularly when videoradiography is used. Small diverticula are less likely to be missed by careful evaluation of lateral and oblique views. The diverticulum is seen to protrude in the posterior midline, generally to the left cervical region (10% to the right), and barium tends to fill the pouch before progressing into the esophagus. In patients with symptomatic Zenker's diverticulum, the pouches usually are more than 2 cm in diameter. Figure 1 illustrates a typical Zenker's diverticulum seen on barium swallow.

Endoscopy is technically difficult and rarely indicated except when cancer is suspected following radiological studies. If endoscopy is indicated for other reasons, it is important to be cautious not to enter the diverticulum and risk perforation.

Manometric evaluation of patients with Zenker's diverticulum is not required from the clinical standpoint, although it is the only technique that will document the increased hypopharyngeal intrabolus pressure. It should be primarily reserved for clinical research. There is no conclusive evidence linking Zenker's diverticulum with gastroesophageal reflux disease. However, patients diagnosed with Zenker's diverticulum should be thoroughly evaluated if they have symptoms such as heartburn or chest pain. Esophageal manometry may confirm the presence of concomitant motility abnormalities contributing to dysphagia.

## TREATMENT

The therapeutic choice in patients with Zenker's diverticulum is dictated by symptoms. Small diverticula discovered by chance in asymptomatic patients do not require any intervention and may be followed by periodic barium swallows. When needed, the only effective treatment of Zenker's diverticulum is surgical. Surgical techniques include, separately or in combination, diverticuloplexy, diverticulectomy, and cricopharyngeal myotomy. Open surgical treatment of Zenker's diverticulum may result in complications such as fistulas, infection, vocal cord paralysis, and aspiration. These complications are quite rare. Endoscopic treatment is emerging as a viable alternative to open surgery. It includes different techniques with or without laser or stapling. There are no comparative studies that allow us to conclude which treatment technique to recommend. At this time, it seems that open surgical procedures are more in favor in the United States, but endoscopic techniques are gaining more advocates as they are being refined.

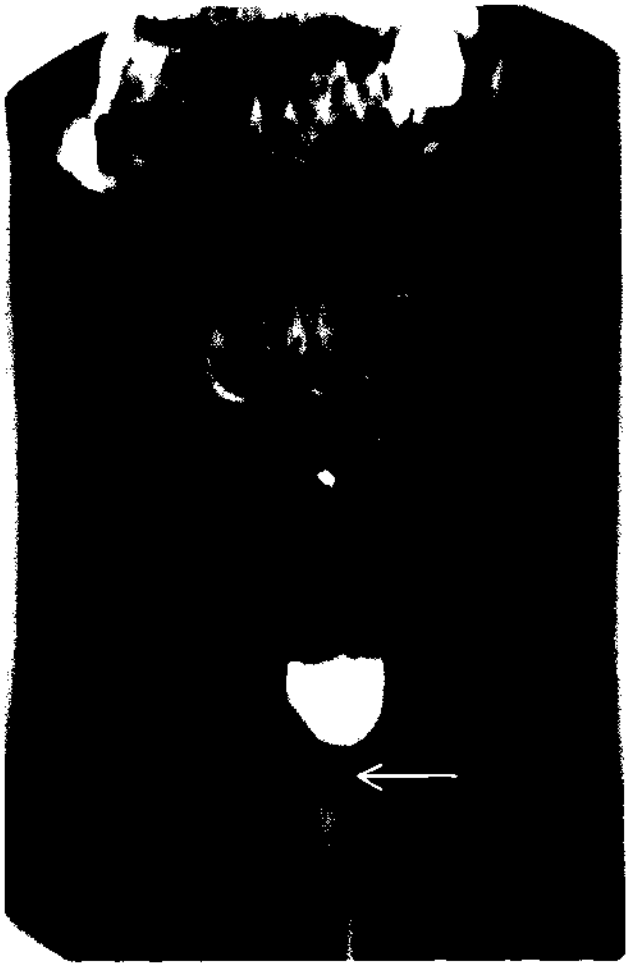

FIGURE 1 Typical Zenker's diverticulum as seen on an anteroposterior view during a barium swallow. The arrow indicates the location of the cricopharyngeal muscle.

## See Also the Following Articles

**Aging • Dysphagia • Esophageal Surgery • Halitosis • Rumination Syndrome**

## Further Reading

Aclukar, E. (1999). Esophageal diverticula. *In* "The Esophagus" (D. O. Castell, J. E. Richter, eds.), 3rd Ed. Lippincott Williams & Wilkins Philadelphia.

Fulp, S. R., and Castell, D. O. (1992). Manometric aspects of Zenker's diverticulum. *Hepato-Gastroenterol.* 39, 123–126.

Mendez, L., Friedman, L. S., and Castell, D. O. (1991). Swallowing disorders in the elderly. *Clin. Geriat. Med.* 7(2), 215–230.

Watemberg, S., Landau, O., and Avrahami, R. (1996). Zenker's diverticulum: Reappraisal. *Am. J. Gastroenterol.* 91(8), 1494–1498.

# GLOSSARY

## A

**ABC-type transporters** Members of a large multigene family of transport proteins expressed in the membranes of epithelial cells. ABC-type transporters contain an ATP-binding cassette, signifying that transport of the particular substrate is energy-dependent. Members of this family play an important role in lipoprotein metabolism by regulating lipid transport (particularly cholesterol and other sterols) both into and out of cells.

**abdomen** The portion of the body that lies between the chest and the pelvis and contains several organs, including the stomach, intestines, liver, spleen, pancreas, kidneys, and bladder.

**abdomino-perineal resection** A surgical procedure involving removal of the rectum and anal sphincter muscles, resulting in the creation of a definitive colostomy. The dissection is achieved through a combined approach, with opening of the abdominal cavity and excision of the anus.

**aberrant crypt foci** Clusters of colonic crypts that typically appear larger and thicker than normal; lumenal shape may also be altered; thought to represent an early precursor of adenocarcinoma, especially when dysplasia is present.

**abscess** A localized collection of pus in a part of the body, surrounded by inflamed tissue.

**absorption** The movement of nutrients and fluid from the intestinal lumen into the lymphatics or bloodstream. This consists of two steps: uptake from the intestinal lumen and transfer from the cytosol of the enterocyte into the lymphatics or portal circulation.

**acalculous** Lacking a gallstone.

**acanthosis nigricans** A disorder involving localized skin hyperpigmentation; appears as velvety hyperpigmentation, primarily in flexural areas. It is usually associated with obesity, type 2 diabetes mellitus, Cushing's syndrome, acromegaly, and the Stein-Leventhal syndrome.

**acetylcholine** The major neurotransmitter of the parasympathetic nervous system; it mediates the secretion of saliva.

**achalasia** Failure to relax; specifically, a motility disorder of the esophagus in which the lower esophageal sphincter does not adequately open during swallowing and contractions in the esophagus are not coordinated.

**achlorhydria** The inability of the stomach to produce hydrochloric acid.

**acinar cells** Pyramidal-shaped epithelial cells in the pancreas that synthesize and secrete digestive enzymes.

**acinus** Functional unit of the exocrine pancreas composed of acinar, centroacinar, and duct cells.

**acromegaly** A condition of increased growth in adults due to the oversecretion of growth hormone (GH). The patient is unusually tall, with an enlarged jaw and large hands and feet. Because this is most commonly related to a pituitary tumor, with tumor enlargement the patient experiences headaches and often visual disturbances.

**active colonic injury** Colonic mucosal disease characterized by neutrophilic inflammation of the mucosa, cryptitis, and crypt abscesses, with or without ulcers.

**acute diarrhea** A diarrheal illness of less than 14 days duration.

**acute fatty liver of pregnancy** Acute liver failure due to microvesicular fatty infiltration of hepatocytes in the third trimester of pregnancy.

**acute intermittent porphyria** One of a group of rare inherited disorders resulting from disturbance of the metabolism of the breakdown products of the red blood cell pigment (porphyrin). A prominent feature is intermittent attacks of abdominal pain.

**acute pancreatitis** An acute condition due to inflammatory disease of the pancreas that typically presents with abdominal pain and elevated pancreatic enzymes in the blood.

**acute tubular necrosis** Abrupt and sustained decline in glomerular filtration rate in response to an acute ischemic or nephrotoxic insult, often characterized by brown tubular casts in the urine.

**adaptation** A process of change in response to environmental conditions; specifically in this context: (1) the process by which the morphology and/or absorptive function of the intestine changes in response to stimuli such as a change in the composition of the diet, the development of diabetes, or a loss of a portion of the intestine; (2) enhancement of the intestinal structure and function to compensate for loss of small bowel length.

**adenitis** Glandular inflammation.

**adenocarcinoma** A malignant neoplasm of epithelial origin that is predominantly glandular or ductal.

**adenoma** A benign or premalignant epithelial tumor in which the cells form recognizable glandular structures or

in which the cells are clearly derived from glandular epithelium.

**adenomatous** Relating to or describing an adenoma.

**adhesion** Close approximation of portal tracts and hepatic veins. Adhesions indicate that loss of parenchyma has occurred, usually through the process of extinction.

**adjuvant chemotherapy** Chemotherapeutic treatment of malignancy administered after surgery or radiotherapy to reduce the risk of relapse.

**adnexal** Describing diseases of the uterine appendages (ovaries, fallopian tubes, and uterine ligaments).

**adynamic ileus** Absence of intestinal motility, often occurring for several days following surgery.

**aerophagia** The fact or condition of swallowing excessive amounts of air.

**afferent** Referring to the nerve components that conduct sensory information from the periphery to the central nervous system. In this context, "sensory" does not necessarily imply sensation.

**aflatoxin B1** A toxic metabolite produced by the fungi *Aspergillus flavus* and *A. parasiticus*, which contaminate improperly stored peanuts, grain, and rice in hot and humid parts of the world.

**agammaglobulinemia** The total absence of antibody.

**agenesis** The absence of an organ.

**agonist** A drug or other substance that binds to a receptor on a cell to induce a response.

**Alagille syndrome** A disease caused by mutations in the Jagged1 gene, resulting in variable manifestations in the liver, heart, spine, eyes, kidneys, face, and other systems.

**alanine aminotransferase** An enzyme that is released from the liver during times of stress and injury; can be measured in serum and plasma.

**alcoholic liver disease** Liver abnormality caused by excessive ingestion of alcohol.

**alkaline phosphatase** An enzyme (pH optimum 9.5–10.5) that hydrolyzes many orthophosphoric monoesters and serves as an important component of intracellular pH buffering.

**allele** The alternate form of the DNA sequence of a gene at a given locus (position of a gene on a chromosome).

**alloantigen** An antigen that occurs in some but not all members of the same species.

**allogeneic** Referring to intraspecies subjects with different genetic constitution.

**allograft** A graft transplanted between genetically nonidentical individuals of the same species.

**allostasis** Dynamic processes involved in the defense of homeostasis that are generated in response to real or perceived stressors/triggers.

**allostatic load** The wear-and-tear damage resulting from chronic overactivity, underactivity, or mismanagement of allostatic systems, all of which can lead to disease and illness.

**alpha cells** Pancreatic islet cells that produce glucagon.

**alveolar air** Expired breath that is representative in composition of the gas present in the alveoli, the smallest divisions of the respiratory tree.

**amebic colitis** Intestinal disease caused by *Entamoeba histolytica*.

**amenorrhea** Absence or abnormal stoppage of the menstrual flow.

**aminotransferases** Hepatocellular enzymes that are released into the bloodstream upon injury of hepatocytes; thus elevated levels serve as markers of liver cell injury. Usually two types, alanine aminotransferase and aspartate aminotransferase

**amphipathic** Denoting molecules that have hydrophobic and hydrophilic domains such that they are surface active and often self-associating to form aggregates (micelles).

**amphiphilic** Functioning in both oil and water; bile salts are amphiphilic in nature because they have both a polar, hydrophilic surface, which contains the hydroxyl groups and a carboxyl group, and a nonpolar, cyclopentanophenanthrene hydrophobic surface.

**ampulla of Vater** The orifice in the duodenum through which the common bile duct and pancreatic duct drain.

**ampullary stenosis** Narrowing of the ampulla, often causing obstruction.

**amyloid** A hyaline eosinophilic substance, as viewed by light microscopy, that is deposited extracellularly in blood vessels and other tissues in a wide variety of disorders. At least 18 distinct proteins that can form amyloid have been identified thus far. All amyloids are fibrillar and look the same under light, polarization, and electron microscopy.

**amyloid P component** A nonfibrillar component of all amyloids that is derived from a normal precursor, serum amyloid P.

**amylopectin** A branched-chain glucose polymer; the major component of dietary starch.

**amylose** A straight-chain glucose polymer present in starch.

**anabolic pathway/signal** Neural circuit/input promoting food intake.

**anaerobe** A microorganism that can live and grow in the absence of oxygen.

**anal sphincters** Rings of smooth muscle or skeletal muscle surrounding the distal rectum and anal canal; contracts to obstruct the passage of feces.

**anal transitional zone** The anal canal segment that lies between the uninterrupted columnar mucosa proximal and the squamous epithelium below.

**anaphylaxis** A hypersensitive reaction triggered by immunological or anaphylatoxin-mediated mast cell mediator release, resulting in vasodilation and smooth muscle contraction. Anaphylactic shock is often fatal.

**anastomosis** A connection created by surgical means between two normally distinct organs or structures that allows the free flow of contents between the two structures.

**anechoic** Without echoes (black); in ultrasonography, generally correlates with a fluid-filled structure.

**angiodysplasia (vascular ectasia)** The most common vascular abnormality of the gastrointestinal tract. Believed to be acquired with aging, it represents the most frequent cause of recurrent lower intestinal bleeding in persons older than 50 years. The likely cause is intermittent, low-grade obstruction of the submucosal veins at the site where the veins penetrate the muscular layer of the colon.

**angiogenesis** The growth of new blood vessels.

**angiography** A radiographic technique by which blood vessels and vascular abnormalities can be visualized following injection of contrast material (dye).

**angioma** An arteriovenous malformation or proliferation, with or without dilation, of the blood vessels.

**angularis** An angular "notch" in the stomach that demarcates the division between the body and antrum of the stomach.

**ankylosing spondylitis** Chronic inflammation of the spine and adjacent joints.

**annular pancreas** A congenital condition in which the pancreas does not rotate normally during embryogenesis, resulting in an extrinsic compression of the second portion of the duodenum.

**anomalous pancreaticobiliary ductal junction** An anatomical variant of the juncture of the common bile duct and pancreatic duct, found in association with gallbladder carcinoma.

**anorexigenic** Acting to suppress the appetite.

**antacid** Any of various medications capable of buffering or neutralizing gastric (stomach) acid.

**antagonist** A drug or other substance that binds to a receptor on a cell to prevent or reverse the response of an agonist.

**anthroponosis** A cycle of infection characterized by transmission between humans.

**anthropozoonosis** A transmissible infection that occurs in animals and humans.

**antibody** A Y-shaped immunoglobulin protein on the surface of B cells that is secreted into the blood or lymph in response to an antigenic stimulus.

**antidepressant** A class of drugs, the primary effect of which is to correct neurotransmitter imbalance in the central nervous system occurring in a major depression. Antidepressants tend to be useful in the functional gastrointestinal disorders, both to treat concomitant anxiety and depression and to reduce pain.

**antiflatulent** A class of drugs effective for the relief of painful bloating or sensations of pressure and fullness, commonly referred to as gas in the digestive tract.

**antigen** Any molecule that can specifically bind to an antibody and elicit an immune response.

**antigen-presenting cells** Cells that have the ability to internalize protein antigens, process them into peptides, and present these peptides on their surface in association with MHC II molecules. The primary antigen-presenting cells are dendritic cells, macrophages, and B lymphocytes.

**antineutrophil cytoplasmic antibodies** Proteins directed against cytoplasmic neutrophil antigens such as proteinase 3 and myeloperoxidase; useful in the diagnosis of small-vessel vasculitis.

**antinuclear antibodies (ANAs)** Autoantibodies that are directed against nuclear antigens and measured by indirect immunofluorescence. Specific ANAs are directed against DNA, histones, components of the spliceosome (Sm, RNP, Ro, and La), and other nuclear antigens (centromere, topoisomerase I).

**antinucleating proteins** Biliary proteins that can inhibit nucleation of cholesterol crystals *in vitro*. Examples include apolipoprotein A-I, apolipoprotein A-II, and immunoglobulin A.

**antiport** Transport that is dependent on the countertransport of another substrate across a membrane barrier.

**anti-*Saccharomyces cerevesiae*** An antibody that recognizes *Saccharomyces cerevesiae* (baker's yeast). It is thought that this antibody represents an altered immune response to bacteria that share cross-reacting epitopes with oligomannosidic cell wall epitopes on baker's yeast.

**antizyme** An enzyme homologue of ornithine decarboxylase, capable of binding and inhibiting it.

**antral sparing** A pattern of gastropathy in which the proximal stomach (fundus and body) is primarily involved and the distal stomach (antrum and pylorus) is relatively or totally free of disease.

**antrectomy** A type of partial gastrectomy in which the stomach's antrum is removed.

**antrum** The distal or lower portion of the stomach.

**anxiety disorder** A condition of excessive anxiety and worry that cannot be controlled and is persistent with a range of symptoms. Mild forms include phobias; more severe forms include panic disorder.

**aphthosis** The occurrence of numerous mucosal ulcers, or apthae. Commonly occurs as an idiopathic disorder or can occur as a part of disorders such as Behçet's disease or Crohn's disease. In Behçet's disease, the aphthae are typically numerous, large, and deep.

**apical membrane** The portion of the intestinal epithelial cell plasma membrane facing the intestinal lumen (the exterior of the body).

**apolipoprotein** A member of a large multigene family of proteins with the ability to bind lipids (cholesterol and triglyceride) in order to facilitate their transport in plasma.

**apoptosis** A mechanism of cell death that is controlled by specific metabolic cell death pathways and that results in fragmentation and condensation of the cell nucleus, without significant inflammation in the surrounding tissue. An evolutionarily conserved method of programmed cell death; also referred to as "cell suicide."

**appendicostomy** An opening that affords access to the large intestine through the tip of the vermiform appendix. It is usually attached to the anterior abdominal wall and is used for irrigation and bowel management in some older

patients with bowel dysfunction following imperforate anus repair.

**appetite** The instinctive desire to eat. Appetite promotes eating behaviors to sustain life.

**area postrema** An area of the medulla where toxins can be detected and vomiting is initiated.

**argentaffin cells** Cells containing a potent reducing agent, usually serotonin, that reduces added silver salts to a black pigment in a manner analogous to development of photographic film.

**argon plasma photocoagulation** The use of ionized argon gas to produce a high-frequency current for the purpose of thermally coagulating tissues.

**arrhythmia** An abnormal rhythm of the heartbeat.

**arrhythmic** Describing an abnormal rhythm.

**arteriomegaly** Diffuse arterial enlargement more than 50% above normal.

**arthralgia** Pain in the joints.

**arthrochalasia** Joint instability or tendency to dislocate.

**ascites** The excessive accumulation of free fluid in the peritoneal cavity.

**aspiration** The inhalation of ingested substances.

**asterixis** Motor disturbance consisting in the failure to actively maintain posture or position.

**ataxia** Coordination problems, such as clumsy or awkward movements and unsteadiness, often beginning with difficulty in walking.

**atopic** A hereditary predisposition to immunoglobulin E-mediated allergic reactions against innocuous antigens (allergens).

**atresia** The congenital absence or closure of a normal body orifice or tubular organ, e.g., esophageal or biliary atresia.

**atrophic gastritis** Loss of the glandular structures and a collapse of the reticulin skeleton of the gastric mucosa, with thinning of the glandular layer of the mucosa and replacement of glands by fibrosis and sometimes by intestinal-type cells.

**attenuated** Describing a less intense form of a condition or disease.

**Auerbach's plexus** A network of neurons located between the circular and longitudinal muscle layers of the gastrointestinal tract; primarily involved with the transmission of motor information between the central nervous system and the peripheral end organ.

**autoantibody** An immunoglobulin directed against a normal cellular component within one's own body.

**autoantigen** A "self-antigen" an agent that stimulates the production of autoantibody.

**autocrine** Describing activity elicited from a nonneuronal cell in response to factors released by that same cell.

**autoimmune** Involving an immune response against the body's own tissues.

**autoinfection** The replication of a nematode parasite within the primary host.

**autonomic** Pertaining to the internal systems in the body (cardiovascular, pulmonary, gastrointestinal) receiving innervation that is not under voluntary control.

**autonomic nervous system** The part of the nervous system in vertebrates that controls involuntary activity.

**autoregulation** A process by which vascular inflow is regulated to maintain total liver blood flow at a relatively constant level.

**autosomal dominant** Describing a Mendelian gene that always manifests phenotypically; all affected individuals have at least one affected parent, and the phenotype affects males and females equally.

**autosomal dominant polycystic kidney disease** A disease characterized by the presence of multiple kidney, and often liver, cysts. The condition is inherited in an autosomal dominant pattern.

**azathioprine (AZA)** An immunosuppressive drug used in refractory ulcerative colitis. It works by interfering with DNA replication and cell proliferation.

**azotemia** Elevation of blood urea nitrogen due to impaired renal function.

## B

**bacillary dysentery** Diarrheal illness caused by bacteria belonging to the genus *Shigella*.

**bacterial overgrowth** An abnormal bacterial proliferation; within the small intestinal lumen, this results in mucosal alterations and changes in bile salt metabolism.

**bacterial translocation** The migration of various bacteria from the gastrointestinal mucosal surfaces to local lymphatic vessels and blood vessels.

**bacteriophage typing** Bacterial typing that differentiates between bacteria or strains of bacteria by their susceptibility to one or more bacteriophages.

**bariatry** A field of medicine or surgery that encompasses the study and prevention of obesity, as well as the evaluation and treatment of obese individuals.

**barium enema** Radiographic examination of the colon and rectum.

**barium sulfate** A white powdery substance used to facilitate radiographic visualization of internal structures of the body.

**Barrett's esophagus** A condition that develops when the normal squamous tissue in the esophagus is repopulated by intestinal epithelium; a premalignant lesion that is believed to occur by metaplastic change during the course of reflux damage to squamous epithelium.

**base** In this context, one of the two functional zones of the gastric unit, found at the bottom of the gastric gland; the site of cells producing the acid and enzymes necessary for breakdown of food in the gastric lumen.

**basement membrane** A specialized, sheet-like, extracellular matrix structure that separates the connective tissue from the epithelia, blood vessels, muscle fibers, and nerves.

**basolateral membrane** The portion of the intestinal epithelial cell plasma membrane facing the blood (interior of the body).

**B-cell gastric lymphoma** A monoclonal proliferation of cancerous B cells that have infiltrated the gastric glands.

**B-cell receptors** Molecules present on B lymphocytes; they contain cell surface immunoglobulin specific for antigen.

**Bence Jones proteins** Free monoclonal immunoglobulin light chains produced and secreted by a single clone of plasma cells.

**bentiromide test** A tubeless pancreatic function test that indirectly measures pancreatic chymotrypsin output using bentiromide as a substrate.

**benzodiazepines** A class of medications with sedating and amnestic effects.

**Bernstein test** A diagnostic test used to determine whether infusion of acid into the esophagus reproduces symptoms of non-cardiac chest pain.

**beta cells** Pancreatic islet cells that produce insulin.

**bezoar** Any of various calculi found chiefly in the gastrointestinal organs and formerly believed to possess magical properties. The prefixes phyto-, tricho-, and lacto- are used to define the major bezoar constituents: vegetable matter, hair, and milk products, respectively.

**bile** Fluid secreted by the liver into the biliary system and subsequently into the gut. Bile is composed of water, organic anionic and cationic substances, electrolytes, and several proteins and lipids. In addition, bile is the route of excretion for many toxic substances. It contains endogenous or exogenous substances that are excreted by the liver, frequently after they undergo hepatic biotransformation.

**bile acids** Molecules that are present in high concentrations in bile and are responsible for its physiological properties. Chemically, bile acids are compounds having the cholane or cholestane nucleus with an acidic group on the terminal carbon of the side chain. One to three hydroxyl groups are present on the nucleus, and there may be an additional hydroxyl group on the side chain. Bile acids are formed in hepatocytes from cholesterol.

**bile alcohols** Molecules that are present in high concentrations in bile in certain species (cartilaginous fish, herbivorous fish, ancient mammals). Chemically, they are compounds with a cholestane nucleus, having a hydroxyl group on the terminal carbon of the side chain.

**bile canaliculus** A domain of polar hepatocytes that connects with the biliary system. It contains many transport proteins that are required for bile formation.

**bile duct** Structure that passes bile from the liver to the gallbladder or to the duodenum.

**bile reflux** The movement of bile from the small intestine (duodenum) into the stomach.

**bile salt** An organic anion that is the ionized form of a bile acid.

**bile salt-dependent bile flow** A component of bile flow that is attributed to the osmotic effect of bile salts secreted into the bile canaliculus.

**bile salt-independent bile flow** A component of bile flow that is not attributed to the osmotic effect of bile salts, and is commonly attributed to the active secretion of electrolytes and other substances.

**biliary atresia** A progressive fibroinflammatory process resulting in obliteration of the extra hepatic biliary duct in infants.

**biliary fistula** An abnormal passage or communication from the biliary system to another location.

**biliary pain** A symptom due to transient obstruction of the biliary tract, including the gallbladder.

**biliary sludge** Microscopic precipitates in bile that can be visualized with ultrasonography or bile microscopy. Can produce symptoms and complications similar to those of gallstones. Also known as microlithiasis or pseudolithiasis.

**biliary stent** A catheter placed within the bile duct to provide patency of the duct.

**biliary system** A collective term for the anatomic area communicating from the liver to the gut. It includes small bile ductules, bile ducts, and the gallbladder.

**biliary tract** A branching tubular network draining bile from the liver into the intestine.

**bilirubin** A porphyrin molecule that is a chemical breakdown product of heme metabolism. Bilirubin is very hydrophobic (insoluble in water) and must be metabolized into its water-soluble glucuronide form prior to secretion into bile. Bilirubin is yellowish, thus, when serum bilirubin levels are elevated, jaundice becomes evident. When bilirubin is oxidized, it becomes biliverdin.

**biliverdin** Oxidized bilirubin (green in color); the major bile pigment in the bile of some fish and mammals. When biliverdin is reduced, it becomes bilirubin.

**Billroth I/II** Reconstructive surgical procedures used after partial gastrectomy in which the remaining part of the stomach is connected to the duodenum or jejunum, respectively.

**binding proteins** Large molecules that circulate in the bloodstream and attach to smaller molecules such as hormones. These proteins tend to prolong the life of the bound hormones by keeping them in the bloodstream.

**binge (binge eating)** Consumption in a discrete time frame (usually $\leq$2h) of an amount of food that is definitely excessive in comparison with the amount of food consumed by most others in similar circumstances. The consumption of large quantities of food at certain celebratory or holiday feasts, for example, is not usually considered to constitute pathological bingeing. A single binge-eating episode may take place at more than one location, but day-long snacking is not a binge.

**bioavailability** The amount of an active agent, such as a drug, that is available at the targeted site after administration.

**bioelectrical impedance analysis** Estimation of total body water by passing low-amperage electrical alternating current through the body and measuring the electrical properties of resistance and reactance.

**biofeedback** The use of electronic or mechanical devices to provide visual and/or auditory information (feedback) on a biological process for the purpose of teaching an individual to control the biological process.

**bioimpedance analysis** Measurement of body resistance and reactance by the use of a fixed high-frequency alternating current; can be used to assess body cell mass and lean body mass indirectly.

**bioimpedance spectroscopy** Measurement of a range of body resistance and reactance by the use of variable high-frequency alternating current.

**biomedical/biopsychosocial models** see DUALISM.

**biopsy** A small tissue sample taken during endoscopy.

**blood-brain barrier** Physiological and anatomical barriers to the free diffusion of larger molecules from the vascular system to the neural circuits of the brain.

**Blue Rubber Bleb Nevus syndrome** A disorder consisting of multifocal venous malformations of the skin, soft tissues/muscles, gastrointestinal tract, or almost any organ.

**Blumer's shelf** A palpable rectovaginal or rectovesical nodularity that may represent metastatic disease from an intra-abdominal or retroperitoneal malignancy.

**blunt injury** A mechanism of injury that deforms tissue on impact and causes tissue disruption when the elastic forces of the tissue are exceeded.

**B lymphocyte** The precursor of an antibody-producing cell (plasma cell); it has a surface antigen receptor that can recognize antigens in solution.

**Bochdalek hernia** Diaphragmatic defect in the postero-lateral chest at the lumbocostal junctions.

**body cell mass** The actively metabolic component of lean body mass, representing approximately 40% of body mass (weight) and consisting principally of skeletal muscle and visceral organs.

**body dysmorphic disorder** A preoccupation with what is perceived to be a defect in one's own body or appearance. The defect is imagined entirely or, if an anomaly is present, the concern is excessive or extreme. The distress related to the misperceived defect is so great that significant social, occupational, or other impairment results.

**body mass index (BMI)** A formulation that describes relative body weight for height; expressed as weight in kilograms divided by height in meters squared, or pounds divided by inches squared. This index provides a good measure of nutritional states including malnutrition, underweight/normal status, overweight, and obese. The BMI is not gender-specific and is relatively independent of height.

**Boerhaave's syndrome** A spontaneous, transmural tear of the esophagus, with free perforation.

**bolus** 1. A rounded mass of food or a pharmacological agent ready to be swallowed. 2. Such a mass passing through the gastrointestinal tract. 3. An intravenously injected dose of a contrast agent, administered rapidly to produce a short contrast effect.

**bombesin-related peptides** Peptides related to the 14-amino-acid peptide, bombesin, which was originally isolated from the skin of the frog, *Bombina bombina*. Many of these peptides (ranatensin, phyllolitorin, litorin) were isolated from the skin of other frogs.

**borborygmi** Rumbling noise produced by the movement of gas in the intestine.

**Borchardt's triad** The combination of pain, unproductive vomiting, and the inability to pass a nasogastric tube in a case of acute gastric volvulus.

**botulinum toxin** A protein produced by *Clostridium botulinum* bacteria, used therapeutically to paralyze or relax the muscle into which it is injected.

**bougie** A mercury-filled rubber tube that is passed by mouth and down the esophagus to dilate or stretch a narrowed segment of intestine.

**bowel ischemia** An acute or chronic syndrome resulting from inadequate blood perfusion of any portion of the small or large bowel.

**bowel resection** Surgical removal of part of the large or small intestine.

**bradygastria** Abnormally slow gastric myoelectrical activity (1.0 - 2.5 cpm).

**brain–gut axis** Bidirectional communication between the central nervous system and the gut via nervous and endocrine pathways to ensure that digestive function is optimal for the overall state of the organism.

**bridging necrosis** A histological pattern of severe liver inflammation in which the inflammatory infiltrate and evidence of hepatocyte damage extend from portal tract to portal tract or portal tract to central vein.

**Brooke ileostomy** Surgical procedure described by Bryan Brooke in which the ileum is passed through an opening in the abdominal wall, with several centimeters protruding and its distal end everted.

**brush border membrane** Apical membrane of the enterocyte, facing the intestinal lumen. This is the site from which uptake of dietary lipid occurs.

**B symptoms** In patients with lymphoma, fever, weight loss, and night sweats; associated with worse prognosis.

**Budd-Chiari syndrome** Obstruction of the hepatic venous outflow at the level of the large hepatic veins or the suprahepatic or intrahepatic segment of the inferior vena cava.

**bulking agents** Macromolecular substances that increase stool bulk and soften feces by water binding. They may be of plant origin (e.g., bran, *Plantago*) or synthetic (e.g., polyethylene glycol). They cannot be split by the enzymes of the human gut, but may be partially digested by the colonic flora.

**bypass** A procedure in which one structure is artificially connected to another so as to circumvent a normally intervening segment of tissue. For example, in a gastric bypass procedure, the stomach is connected to the second portion of the small intestine so that food circumvents the main part of the stomach and the first portion of the small intestine.

## C

**cachexia** Severe malnutrition.

**caerulein** An analogue of cholecystokinin that, because it is more stable, is used for secretagogue-induced pancreatitis.

**cag pathogenicity island** (*cag* PAI) A group of approximately 40 genes present in the genomes of some *Helicobacter pylori* strains. Strains with the *cag* PAI cause more inflammation and the presence of this pathogenicity island is associated with an increased risk of developing gastric cancer or peptic ulcer disease.

**calcitonin** A thyroid hormone that acts to regulate calcium levels in the blood and to stimulate bone mineralization.

**calcitonin receptor-like receptor** One of the three proteins that form the calcitonin gene-related peptide receptor complex (the other two proteins are the receptor-associated membrane protein-1 and the receptor component protein). The calcitonin receptor-like receptor consists of seven transmembrane domains, is coupled to G proteins, and serves as the receptor protein that recognizes calcitonin gene-related peptide as ligand.

**calculous** Relating to or denoting a calculus.

**calculus** (*pl.* **calculi**) An abnormal concretion (stone), usually containing mineral salts; e.g., a gallstone.

**calmodulin** An intracellular high-affinity calcium-binding polypeptide forming a calcium/calmodulin complex that regulates ion transport through the modification of cellular regulatory proteins.

**canaliculus** (*pl.* **canaliculi**) A space formed between the apical membranes of hepatocytes, into which canalicular bile is secreted; the smallest unit of the biliary tract.

**canals of Hering** Structures lined by both cholangiocytes and hepatocytes; the most peripheral portion of the biliary system.

**capacitative $Ca^{2+}$ entry** Influx of extracellular $Ca^{2+}$ across the cellular plasma membrane following the depletion of intracellular $Ca^{2+}$ stores.

**capsaicin** A natural ingredient of hot peppers of the genus *Capsicum*, the pungent ingredient of many "hot" and spicy foods. A subtype of primary afferent neurons is sensitive to capsaicin; at low doses, capsaicin stimulates these neurons and is toxic to the neurons at high doses or after prolonged treatment.

**capsule wireless endoscopy** The use of a small camera containing a capsule that is ingested to evaluate the gastrointestinal tract. Typically used to investigate bleeding sources in the small intestine.

**carbohydrate intolerance** Clinical symptoms induced by the ingestion of specific forms of carbohydrate (e.g., lactose intolerance, sucrose intolerance, fructose intolerance) or carbohydrates in general.

**carbohydrate malabsorption** Poor absorption of any given carbohydrate; detected by specific testing (e.g., lactose absorption test, lactose breath test).

**carcinogenesis** The process in which normal cells develop into cancerous ones.

**carcinogenic** Of or pertaining to the ability to cause the development of cancer.

**carcinoid (tumor)** A tumor arising from the neuroendocrine cells found throughout the body; the most frequent origin is from the gastrointestinal tract or bronchus. Many, but not all, release neurohormonal agents such as serotonin.

**carcinoma** Any cancer that arises from the epithelium.

**carcinomatosis** The presence of widespread peritoneal implants from tumor.

**cardia** The upper part of the stomach just below the esophagus.

**Caroli's disease** Congenital cystic dilatation of the intrahepatic bile ducts.

**carrier** 1. A person who is a heterozygote for a mutant allele. 2. The human or animal host for a certain pathogen.

**carrier-mediated membrane transport** Mechanism for transporting a substrate that involves a defined protein system located at the plasma membrane of the cell.

**caseating granuloma** An aggregation of granulofibrillar necrotic material, and sometimes eosinophilic granules.

**case-control study** An epidemiological study design in which exposures are compared between a group of individuals with the disease of interest (cases) and a group of individuals without the disease (controls); also called a **retrospective study**, since the exposure information is collected after a diagnosis has been established.

**caspases** Proteases that operate in a cascade to initiate programmed cell death.

**catabolic pathway/signal** A neural circuit/input reducing food intake.

**catecholamines** A goup of physiologic substances, mainly epinephrine, norepinephrine, and dopamine; they act as neurotransmitters in the functioning of the sympathetic nervous system.

**cathartic** An agent that results in the purging of bowel contents.

**cationic trypsinogen** The precursor form of trypsin defined by its cationic (net positive) charge.

**causality assessment** An analytical method allowing evaluation of the relationship between drug administration and the occurrence of a liver injury.

**cautery** A procedure that delivers heat to body tissue to destroy it.

**cavernous hemangioma** A benign vascular malformation presenting as a vascular mass in the liver. These may show cystic characteristics.

**CCK** See CHOLECYSTOKININ.

**CDE diet** Choline-deficient diet supplemented with ethionine; this diet induces pancreatitis in female mice.

**celiac disease** An autoimmune disorder affecting the small intestine; caused by abnormal responses to certain grains, it leads to small intestinal mucosal damage and nutrient malabsorption.

**celiac sprue (gluten-sensitive enteropathy)** A malabsorptive disorder in which there is an atrophic and inflamed proximal small intestinal mucosa that usually improves morphologically and clinically on treatment with a gluten-free diet but relapses when gluten is reintroduced.

**cell cycle** The series of four phases that a dividing or proliferating cell goes through. $G_1$ is the first of two growth phases and is the longest portion of the cell cycle. S phase is the period during which a cell's genetic material is replicated, $G_2$ is the second growth phase, and M phase is when a cell divides into two genetically identical cells.

**centroacinar cells** Terminal duct cells bordering the acinar lumen that secrete bicarbonate into the lumen.

**centromere** The site on a chromosome that pulls the chromosome toward one of the poles of the spindle during mitosis and meiosis; it is also the point of attachment of the sister chromatids.

**cerebral edema** Excessive extracellular water in the brain, leading to increased intracranial pressure.

**ceruloplasmin** Copper-containing serum glycoprotein produced mainly in the liver; it binds six copper atoms per molecule of protein.

**cestode** A parasitic segmented flatworm of the class Cestoidea in the phylum Platyhelminthes; also known as a tapeworm.

**cevimeline** A cholinergic drug that stimulates secretion of most exocrine glands, including lacrimal and salivary glands.

**chemical coding** The particular combination of neurotransmitters, neuropeptides, and other neuronal chemical markers characteristic of a particular class of neuron.

**chemical splanchnicectomy** Chemical blockage of the celiac nerve plexus, performed either intraoperatively or percutaneously, in order to palliate pain associated with pancreatic adenocarcinoma.

**chemokine** A chemotactic cytokine, i.e., a secreted polypeptide hormone that promotes the migration of cells along a concentration gradient to activate immune responses and other mechanisms.

**chemoprevention** The use of chemical compounds to prevent, inhibit, or reverse carcinogenesis before dysplastic epithelial cells invade across the basement membrane; may refer to either nutritional or pharmaceutical agents.

**chemoreceptors** Molecules on sensory neurons that recognize specific chemical substances in the extracellular milieu and signal changes in the concentration of the specific substance.

**chemosensory systems** Biological systems that detect soluble and volatile chemicals.

**chemotherapeutics** A class of anti-neoplastic drugs used to treat leukemic cancers, solid tumor cancers, or other cancers.

**Child-Pugh classification (score)** Assignment of the severity of cirrhosis based on clinical and laboratory parameters, including encephalopathy, ascites, bilirubin, albumin, and prothrombin time; in order of increasing severity of cirrhosis, classes A, B, and C. Also used to predict which patients with end-stage liver disease will survive a major abdominal surgery.

**chlamydospore** A thick-walled fungal spore, considered a survival structure in most fungi.

**cholangiocarcinoma** A malignant transformation of cholangiocytes that carries a poor prognosis.

**cholangiocytes** Epithelial cells that line the bile ducts.

**cholangiogram** A radiograph of the gallbladder and bile ducts; may be performed intraoperatively by either an open or a laparoscopic technique.

**cholangiography** Radiographic examination of the bile ducts with a contrast medium.

**cholangitis** Inflammation and infection of the bile duct and biliary system.

**cholecystectomy** Removal of the gallbladder either by laparoscopic technique or open abdominal surgical incision.

**cholecystitis** Inflammation of the gallbladder.

**cholecystokinin (CCK)** A peptide hormone produced by endocrine cells of the upper small intestine; secreted on ingestion of a meal; the major hormone responsible for pancreatic enzyme secretion and gallbladder contraction.

**cholecystokinin-releasing peptide** A trypsin-sensitive peptide whose presence in the lumen of the intestine leads to the release of cholecystokinin from intestinal enteroendocrine cells.

**cholecystostomy** Drainage of the gallbladder, usually by percutaneous tube placement, in patients with cholecystitis who are too unstable to tolerate a traditional cholecystectomy.

**choledochal cyst** A congenital, cystic structure arising from the biliary tree, often in association with abdominal pain and jaundice.

**choledochocele** A cystic biliary dilatation within the wall of the duodenum.

**choledochoenterostomy** Surgical establishment of a communication between the common bile duct and any part of the intestine.

**choledochojejunostomy** Surgical procedure in which the common bile duct is connected to the jejunum.

**choledocholithiasis** Stones in the common bile duct.

**choledochoscopy** Endoscopic examination of the common bile duct.

**cholehepatic shunt** A mechanism to explain hypercholeresis (greatly increased bile flow) resulting from hepatic secretion of unconjugated bile acids.

**cholelithiasis** The presence or formation of gallstones.

**cholera** A diarrheal disease caused by toxigenic strains of *Vibrio cholerae*.

**choleretic** Causing an increase in bile flow. A choleretic substance will stimulate the formation and secretion of bile.

**cholerrheic diarrhea** Diarrhea resulting from the presence of malabsorbed bile acids.

**cholestasis** Decrease or stoppage of bile flow, typically associated with increased bilirubin, increased bile salts, or both. Elevations typically result in the visible signs of jaundice.

**cholestatic liver injury** Clinical and biological patterns reflecting impaired bile flow. The syndrome can be isolated (pure cholestasis) or associated with inflammation (cholestatic hepatitis).

**cholesterol** A sterol that is present in cell membranes. Cholesterol is white and insoluble in water. It has the cholestene nucleus with a double bond at $C_5$–$C_6$ nucleus and a hydroxy group on the third carbon atom.

**cholesterol saturation index** In a given bile sample, the ratio of the actual amount of cholesterol to the maximum cholesterol-carrying capacity of that sample, determined *in vitro*. Bile with a cholesterol saturation index greater than 1 is considered supersaturated.

**cholesterol supersaturation** A state in which the amount of cholesterol in bile exceeds the cholesterol-carrying capacity of the biliary lipids; a prerequisite for cholesterol gallstone formation.

**cholic acid** Primary bile acid; very common in many mammals. Chemically, it is a $C_{24}$ bile acid with hydroxyl groups at carbons 3, 7, and 12.

**choreoathetosis** Abnormal movements of the body of combined choreic and athetoid pattern.

**chromoendoscopy** The spraying of a dye that can be seen endoscopically and that may highlight surface irregularities or specific histologic features.

**chromogranin** A protein present in cellular storage granules or vesicles containing bioactive amines such as histamine and norepinephrine.

**chronic active gastritis** A condition of chronic inflammation of the gastric mucosa associated with neutrophilic infiltration.

**chronic colonic injury** A colonic mucosal disease characterized by alterations in the cellular components and architecture, suggestive of ongoing injury.

**chronic diarrhea** A diarrheal illness of greater than 14 days duration. Chronic diarrhea in children can be due to either infectious or noninfectious processes. Evaluation for a specific etiology is indicated. Management of comorbid conditions such as poor growth or malnutrition is essential.

**chronic intestinal pseudo-obstruction** A syndrome due to a failure of intestinal propulsion and characterized by a clinical picture resembling mechanical obstruction, in the absence of any lesion occluding the lumen of the gut.

**chronic liver disease** Ongoing injury to the liver lasting at least 6 months.

**chronic pancreatitis** A persistent inflammatory disease of the pancreas characterized by irreversible morphological change that often causes pain or loss of exocrine function or both.

**chronic viral hepatitis** Infection with hepatitis B or hepatitis C virus lasting more than 6 months.

**chylomicron** The largest lipoprotein particle, containing a central core of triglyceride, cholesterol ester, and phospholipid surrounded by a phospholipid coat and apolipoproteins. This is the particle secreted by the intestine following lipid absorption; it allows the transport of triglyceride and cholesterol out of the enterocyte, into the lymphatic circulation, and ultimately into plasma.

**chyme** A slurry of partially digested foods and liquids that is transiently present in the intestines following a meal.

**ciliated hepatic foregut cyst** A solitary cystic lesion lined with ciliated, pseudo-stratified columnar epithelium.

**circumventricular organs** A group of brain areas where blood vessels are not equipped with the blood-brain barrier, thus allowing the entry of small peptides into the brain.

**cirrhosis** A degenerative disease of the liver that results in damage to hepatic parenchymal cells and decreased blood flow to the liver; characterized by the development of fibroids and nodes.

**cis-acting/trans-acting elements** Factors that regulate gene expression in eukaryotic cells, by the interaction of specific proteins (trans-acting elements) with specific short nucleotide sequences (cis-element motifs), usually in the promoter region of genes.

**class II major histocompatibility complex** Highly polymorphic cell surface molecules primarily expressed on B lymphocytes, macrophages, and dendritic cells; they are involved in peptide antigen presentation to $CD4^+$ T lymphocytes (helper T cells), which stimulates humoral immunity and macrophage activation.

**cloaca** A common channel for passage of fecal, urinary, and sexual material, typically seen in lower vertebrates. In humans, it denotes an embryologic abnormality in which the terminal hindgut fails to divide into the rectum, bladder, and genital primordium.

**coagulation** The natural process by which blood clots to reduce or prevent bleeding.

**coagulopathy** An alteration in the normal clotting mechanisms of blood.

**cobalamin** The entire vitamin $B_{12}$ molecule except for the cyanide moiety, which may be substituted for by other organic ligands (methyl, adenosyl) and still retain full activity.

**coelom** The body cavity of the mammalian embryo.

**cognitive behavioral therapy** The therapeutic approach of adding to behavioral interventions (e.g., relaxation and behavior management techniques) strategies such as cognitive restructuring; for example, a therapist may evaluate a patient's cognitive interpretation of bodily sensations and teach how cognition impacts affective experience and behavior.

**cohort study** An epidemiological study design in which a group of exposed individuals and a group of nonexposed individuals are followed forward in time to compare incidence rates for the disease of interest; also called a **prospective study**, since the exposure information is collected before a diagnosis has been established.

**cold ischemia** A technique to slow the metabolism of an organ in order to reduce oxygen consumption; used in the transplant setting and during organ harvesting and preservation.

**coliforms** Gram-negative aerobic rods that are part of the family *Enterobacteriacae* and are found in normal bowel flora.

**colitis** Any inflammation of the colon, which can be transmural or confined to the mucosa, which may be acute or chronic, and which may resolve, resolve and recur, or be persistent. Colitis usually presents clinically as bloody diarrhea, abdominal cramping, and tenesmus.

**colitis cystica profunda** A benign pathologic condition characterized by mucin-filled cysts located deep to the muscularis mucosae.

**collagen** Strong, elastic, fibrous protein; the foundation of all connective tissues in the body.

**collagenous colitis** A condition of chronic colitis, characterized by thickening of the collagen layer beneath the surface epithelium. Typically seen in middle-aged and older women with watery diarrhea.

**Collis gastroplasty** A procedure that "lengthens" the esophagus by transforming a portion of the upper stomach into an esophageal extension.

**colonic motility** Patterned activity of the musculature of the colon responsible for propulsion and mixing of the luminal contents.

**colonic transit** Measurement of the time it takes for inert markers to pass through the colon and anorectum, traditionally measured while the subject consumes a high-fiber diet and uses no laxatives.

**colonoscope** A fiber-optic flexible endoscope that permits visual examination of the entire colon.

**colonoscopy** Examination of the colon, rectum, and terminal ileum using a flexible videoendoscope (**colonoscope**) introduced through the anus, usually after preparation of the patient with laxatives to clear the colon of feces.

**colorectal adenocarcinoma** A malignant neoplasm of the colon or rectum.

**colorectal adenoma** A benign neoplasm of the colon or rectum with malignant potential.

**colorectal polyp** A growth protruding from the mucosal surface into the bowel lumen.

**columnar epithelium** A classification of epithelium composed of a type of cell whose height is larger than its width.

**commensalism** A state of bacterial colonization that results in either no damage or clinically inapparent damage to the host, though it can elicit an immune response.

**common bile duct** The duct formed by the juncture of the cystic duct and common hepatic duct, permitting the flow of bile from the liver and gallbladder to the small intestine.

**complex lipid** A term for the major lipid products of intestinal and hepatic lipid assembly. The major classes of neutral lipid include triglyceride and cholesterol ester, whereas complex polar lipids are represented by phospholipids.

**compulsion** A repetitive, seemingly involuntary, nonpreventable behavior.

**computer-aided detection** The use of software to assess and locate areas of concern in scanned images, alerting a radiologist to evaluate an area that may represent a potential lesion.

**computed radiography** A radiographic system using computers to capture and digitize an image rather than print it on film.

**computed tomography** (CT) A radiographic technique allowing visualization by computer reconstruction of a plane or section through the body. Also, **computerized tomography**.

**confluent** Describing cells in culture at high density and in contact with one another so that there are no empty spaces.

**conformational diseases** A group of disorders resulting from gene mutations affecting the proper folding and three-dimensional structure of intracellular proteins, leading to changes in protein interactions, abnormal intracellular accumulations, and altered function.

**confusional syndrome** Disturbed orientation in regard to time, place, or person, sometimes accompanied by disordered consciousness.

**congenital diarrhea** A group of diarrheal illnesses that are present from birth. Congenital diarrhea can be the result of either a specific genetic defect in a secretory or absorptive pathway or abnormal intestinal development.

**conjugation** In metabolism, the addition of a molecule that renders a lipophilic molecule more hydrophilic and usually makes it more water soluble. Molecules commonly used for conjugation include sulfate, glucuronic acid, glutathione, glycine, and taurine.

**conscious sedation** A level of sedation in which the patient is relaxed, comfortable, and perhaps in a state of light sleep. The patient is easily arousable and able to protect his or her airway.

**constipation** A symptom complex commonly defined as characterized by decreased bowel movement frequency, difficulty in initiating passage of feces, passage of firm or small-volume feces, or a feeling of incomplete evacuation.

**constrictive pericarditis** Fibrous scarring and noncompliance of the pericardium that results from causes of chronic pericarditis, including tuberculosis, malignancy, or radiation.

**contrast-enhanced computed tomography** Images obtained with intravascular and intralumenal contrast material. This is the preferred scanning protocol for most intra-abdominal pathology.

**contrast media** Substances used to facilitate radiographic visualization of internal structures of the body.

**cotransporter** An ion transporter that carries more than one ion in the same direction across the outer cell membrane.

**counterregulatory hormones** The various hormones of intermediary metabolism, including growth hormone, catecholamines, cortisol, and glucagon, that counter the effects of insulin to lower glucose levels.

**Courvoisier's sign** A nontender, palpable gallbladder, often associated with a malignant obstruction of the common bile duct.

**creatinine-height index** A calculation of a 24-hour urinary excretion of creatinine; an indirect measure of skeletal muscle, which, when related to height and gender, can be used to estimate the degree of protein calorie malnutrition.

**cricopharyngeous** Describing striated muscle attached to the posterior aspect of the lamina of the cricoid cartilage; it forms the major component of the upper esophageal sphincter.

**Crigler-Najjar syndrome** A syndrome of severe unconjugated hyperbilirubinemia that presents as congenital familial nonhemolytic jaundice and is related to a lack of ability to conjugate bilirubin, as well as a blockage in bilirubin excretion from the hepatocyte.

**Crohn's disease** A disease of chronic inflammation, potentially involving any portion of the gastrointestinal tract but with a propensity for the terminal ileum. The etiology of this disease is incompletely understood. Crohn's disease is included with ulcerative colitis in the category "inflammatory bowel disease."

**cross-sectional imaging** Radiologic studies such as computed tomography or magnetic resonance imaging, which display the relevant anatomy as a series of "slices" from which three-dimensional relationships can be inferred.

**cryoglobulinemia** The most common extrahepatic manifestation of chronic hepatitis C. Cryoglobulins are detected in lab tests based on their precipitation at cold temperatures; symptomatic disease is uncommon (less than 1% of patients) and results from local deposition of immune complexes.

**cryosurgery** An ablative procedure in which subzero liquid nitrogen is injected into the hepatocellular cancer, with a goal of killing the tumor cells.

**crypt of Lieberkühn** A zone of proliferation in the small intestine, located underneath the villi. Crypts provide the cells that replace the epithelium of the villi of the small intestine.

**cubilin** A multifunctional protein in the apical (luminal) membrane of intestinal and renal cells; composed of multiple closely related repeating units, two of which are responsible for binding the IF-Cbl complex.

**cyclic GMP** An intracellular signaling molecule that is produced by the cell surface receptors for guanylin and uroguanylin in target cells. Responsible for mediating cellular responses to these peptide hormones.

**cyclooxygenases** A family of enzymes, of which at least two isoforms exist, cyclooxygenase-1 and cyclooxygenase-2. They act on arachidonic acid to produce a number of compounds, including prostaglandins and thromboxane.

**cyclosporin** A calcineurin inhibitor that suppresses T helper cell responses to interleukin-1 (IL-1), thus blocking the immune response via its effect on calcineurin-mediated IL-2 mRNA transcription and production; used to treat acute severe refractory ulcerative colitis.

**cyst** 1. A closed cavity or sac lined with epithelium, containing fluid or semisolid material. 2. an environmentally stable form of the life cycle of a protozoan that reproduces asexually. The cyst has a hard outer wall and is involved in the transmission of the organism from one host to another.

**cystadenocarcinoma** A malignant cystic lesion derived from glandular epithelium.

**cystadenoma** A benign cystic lesion derived from glandular epithelium.

**cystectomy** The surgical removal of the urinary bladder.

**cystic duct** A gallbladder duct that connects to the common bile duct.

**cytochrome P450 system** A group of enzymes that control the concentrations of many endogenous substances and drugs, so named because of their absorbance maximum at 450 nm under laboratory conditions. These enzymes are found mainly in the liver (hepatic microsomal enzymes) and gut.

**cytokines** A large class of relatively low-molecular-weight proteins produced by leukocytes and other cell types with a broad spectrum of functional activities, mainly regulating inflammatory and immune responses.

**cytolytic liver injury** Clinical and biological patterns reflecting liver cell necrosis.

**cytoskeleton** The inner framework of the cell. It maintains and adapts cell shape, makes directed migration possible, and provides strength and organization for cellular functions.

**cytosol** The fluid component of cytoplasm, excluding organelles.

**cytotoxic** Describing an agent that destroys or damages cells.

**cytotoxins** Proteins produced by cytotoxic T lymphocytes; they participate in the destruction of target cells.

## D

**deconjugation** The dissociation of the chemical bond between two chemical compounds.

**definitive host** The host in which a parasite achieves sexual maturity.

**deglutition** The process of swallowing.

**Delorme procedure** A perineal approach to the repair of rectal procidentia in which there is circumferential mucosectomy followed by longitudinal plication of the rectal wall, and mucosal reapproximation.

**demilunes** Crescent-shaped groups of serous secretory cells at the ends of mucous end-pieces.

**denervation** The act or procedure of cutting a nerve.

**depressive disorder** Depression accompanied by reduced activity, reduced appetite, changes in sleep pattern, feelings of fatigue or loss of energy, and feelings of guilt or worthlessness. Suicidal ideas occur in severe forms.

**dermatomyositis** Inflammatory myopathy manifested by symmetric proximal muscle weakness and skin rash, often in association with malignancies.

**dermatosparaxis** A condition of skin fragility.

**diabetes ketoacidosis** A syndrome consisting of hyperglycemia, ketosis, and acidemia.

**diabetes mellitus** A chronic metabolic disorder in which utilization of carbohydrate is impaired and that of lipid and protein is enhanced; it is caused by an absolute or relative deficiency of insulin and is characterized, in more severe cases, by chronic hyperglycemia, glycosuria, water and electrolyte loss, ketoacidosis, and coma.

**diabetic neuropathy** A generic term for any short-term and long-term nerve dysfunction in diabetes, characterized by generalized slowing of conduction and an increased threshold for excitation in the peripheral and autonomic nerves.

**diamine oxidase** An enzyme (also known as amine oxidase or histaminase) secreted by enterocytes; it plays an important role in the breakdown of histamine and polyamines.

**diaphoresis** Excessive perspiration.

**diaphragm** The muscular partition that separates the abdomen and thorax; a primary muscle used in breathing.

**diarrhea** The frequent passage of loose, watery stool. A symptom of several gastrointestinal disorders affecting water and electrolyte transport.

**diarrheagenic *Escherichia coli*** A group of *Escherichia coli* strains that cause diarrhea; two strains are important causes of diarrhea in international travelers to tropical and semitropical areas: enterotoxigenic *E. coli* and enteroaggregative *E. coli*.

**diathermy** Local elevation of temperature within the tissues, produced by high-frequency current, ultrasonic waves, or microwave radiation.

**dietary fats** Substances, predominantly triglycerides, that consist of acyl chains or fatty acids linked to glycerol through ester bonds.

**dietary fiber** The portion of plant food that resists digestion, composed of either insoluble or soluble components. Insoluble fiber retains water within the cellular structures, whereas soluble fiber stimulates growth of colonic bacteria; both actions increase fecal mass.

**Dieulafoy's lesion** A rare cause of massive gastrointestinal bleeding; results from a large artery in abnormally close contact with the lining of the stomach or small intestine.

**differentiation** The process of a cell maturing and acquiring a particular, specific function within the body, usually accompanied by a loss of the ability to proliferate.

**diffuse esophageal spasm** Disordered esophageal peristalsis; diagnosed by manometry; frequently associated with chest pain or dysphagia of unknown origin.

**digenean** Having two hosts.

**digestion** A process in which ingested nutrients are broken down into smaller components to facilitate their absorption by the small intestine.

**digestive system** The collective organ system responsible for digestion and absorption.

**digital fluoroscopy** The process of capturing and transmitting fluoroscopy information to a computer rather than intensifying it and using it to expose film.

**digital rectal examination** The use of the finger to manually inspect the anus, anal canal, and lower rectum for palpable or visual lesions.

**dimer** A molecule made up of two identical units.

**dipeptidyl peptidase IV** A proteolytic enzyme occurring in the plasma membranes of many cells, including vascular endothelial cells, as well as in a soluble form in plasma. It is responsible for rapid inactivation of the glucagon-like peptides 1 and 2.

**distal colon** Anatomic subsite of the colorectum that includes the descending colon, sigmoid colon, and rectosigmoid colon; may sometimes include the rectum as well.

**divalent metal transporter-1 (DMT1)** A protein located in the apical villous surface of enterocytes; it imports non-transferrin-bound iron from the small bowel lumen to the enterocyte cytoplasm.

**diversion colitis** A characterisitic mucosal inflammation that typically occurs whenever the colon is excluded from the intestinal stream and that subsides when intestinal continuity is restored.

**diversion proctitis** Inflammation and friability of the colonic mucosa after exclusion of a distal segment of colon from the fecal stream.

**diverticula** See DIVERTICULUM.

**diverticula of the colon** Herniations of the mucosa and submucosa though or between fibers of the major muscle layer (muscularis propria) of the colon.

**diverticulitis** Inflammation of a diverticulum that may undergo perforation with abscess formation.

**diverticulosis** The presence of multiple diverticula of the intestine, common in middle age; the lesions are acquired pulsion diverticula.

**diverticulum (*pl.* diverticula)** A circumscribed pouch or sac of variable size that may occur normally, as in embryologic development of the respiratory bud off the foregut, or pathologically, resulting from the herniation of the lining mucous membrane through a defect in the muscular wall of a tubular organ.

**DNA caretaker gene** A sequence on a gene encoding a product that normally maintains the fidelity of genomic DNA.

**DNA fingerprinting** A laboratory method elaborating a battery of molecular biology techniques in order to generate a pattern of DNA restriction fragments that is unique to an individual or a microbe. In the latter case, one of the aims is microbial source tracking.

**DNA mismatch repair** A process in which certain proteins recognize and correct errors made by DNA polymerase during DNA replication.

**Dogiel Type I neurons** Enteric neurons with multiple short dendrites and a single long axon.

**Dogiel Type II neurons** Multipolar enteric neurons with smooth cell bodies and multiple long and short processes in a variety of configurations.

**Doppler** Frequency shift caused by blood flow.

**dorsal root ganglia** A series of paired neural ganglia adjacent to the spinal cord; they contain the neuronal cell bodies of capsaicin-sensitive primary afferent nerves as well as other afferent nerves.

**dorsal vagal complex** The parasympathetic center in the brainstem (medulla oblongata) where sensory signals from the gut and motor outflow to the gut are integrated.

**double-bubble sign** A radiographic appearance signifying duodenal obstruction; it consists of large air collections in the stomach and in the duodenum, without visualization of gas more distally in the gastrointestinal tract.

**double duct sign** A radiographic sign seen on computed tomography scan or endoscopic retrograde cholangiopancreatography that results from the simultaneous obstruction of the common bile duct and pancreatic duct by a mass from the head of the pancreas.

**down-regulating** The process of reducing the level of a cellular product by inhibiting its synthesis, degrading it, or transporting it out of the cell.

**drug-induced lupus erythematosus** A distinct form of lupus caused by sustained exposure to certain drugs (procainamide, phenytoin, and isoniazid are the commonest) associated with the production of anti-histone antibodies and clinically with fever, arthralgia, myalgia, rash, and serositis and the absence of renal or central nervous system involvement.

**dual-energy X-ray absorptiometry** A noninvasive technique used to assess body composition, specifically bone and soft tissue.

**dualism** A concept, first proposed by Descartes, that separates mind and body. Cartesian dualism (the biomedical model) is the dominant model of illness in Western society and is challenged by the contemporary biopsychosocial model which emphasizes the interplay of biological, psychological, and social factors.

**Dubin-Johnson syndrome** A conjugated hyperbilirubinemic disorder caused by an inherited deficiency of the MRP2 canalicular transporter.

**duct of Santorini** A small accessory pancreatic duct located cephalad to the main pancreatic duct.

**duct of Wirsung** The main pancreatic duct.

**ductopenia** Paucity of the bile ducts.

**dumping syndrome** An abnormally rapid emptying of stomach contents into the small intestine, associated with symptoms of dizziness, rapid heart rate, sweating, nausea, and diarrhea occurring mainly after a meal.

**duodenal** Relating to, located in, or involving the duodenum (first portion of the small intestine).

**duodenal atresia** Congenital condition in which the embryonic cells lining the duodenum fail to completely resorb, resulting in a blockage in the duodenum (stricture).

**duodenal cytochrome b (Dcytb)** A ferric reductase found in the brush border membrane of proximal intestinal enterocytes. Dcytb converts the poorly absorbed ferric form of iron ($Fe^{3+}$) to the ferrous form ($Fe^{2+}$) that is transported into the cells by divalent metal ion transporter-1.

**duodeno-jejunostomy** A surgical procedure in which the proximal duodenum is attached side-to-side to the proximal jejunum in order to bypass an obstructing lesion in the mid- to distal duodenum.

**duodenum** The first portion of the small intestine, located between the stomach and the jejunum.

**duplication cysts** Congenital intestinal duplications that can be found in the walls of the esophagus, stomach, or duodenum.

**dyschezia** Difficulty in evacuation of stool, including straining, painful defecation, and incomplete evacuation.

**dysgeusia** Difficulty in tasting.

**dyslipidemia** Abnormalities of plasma lipoproteins that include both higher and lower levels of certain lipoproteins.

**dysmenorrhea** A condition marked by painful menstruation.

**dyspareunia** Difficult or painful sexual intercourse.

**dyspepsia** A general term for various symptoms originating in the upper gastrointestinal tract, including upper abdominal pain/discomfort, early satiety, postprandial abdominal bloating/distension, and nausea with or without vomiting.

**dyspeptic** Affected with dyspepsia.

**dysphagia** A symptom in which the patient experiences trouble or difficulty in swallowing. When the symptom occurs with solids only, it usually reflects a lumen-narrowing obstruction and when it occurs with both liquids and solids, it usually reflects an oropharyngeal or esophageal motor disorder.

**dysplasia** A constellation of histological abnormalities that suggest that one or more clones of cells have acquired genetic damage, rendering them neoplastic and predisposed to malignancy. When seen in a patient with a chronic inflammatory disorder (e.g., Barrett's esophagus, chronic gastritis, ulcerative colitis, Crohn's disease), the finding of dysplasia serves as a marker that the patient has or is especially apt to develop adenocarcinoma.

**dyspnea** Difficult or labored breathing.

**dysuria** Painful urination.

## E

**early gastric cancer** A term for cancer involving the mucosa or submucosa (with or without lymph node involvement).

**Echinococcus** A genus of tapeworms, capable of causing hydatid cysts in humans.

**ectasia** Arterial dilation less than 50% of expected normal diameter.

**ectodomain** The extracellular portion of a molecule that spans the plasma membrane.

**ectopic** Out of place; not in a proper position.

**edema** The accumulation of excessive watery fluid in tissues or serous cavities.

**edrophonium** A drug that when injected stimulates contraction of smooth muscles (e.g., esophageal smooth muscle).

**efferent** Describing the nerves that carry impulses away from the brain or spinal cord to the periphery.

**efferent trafficking** The outflow of information to the gut from the brain and spinal cord.

**Ehlers-Danlos syndrome** A heterogeneous group of heritable collagen disorders characterized by joint hypermobility and increased skin elasticity and tissue fragility.

**elasticity imaging** A process in which the stiffness of a tissue under compression is turned into an image.

**electrical control activity** Ongoing spontaneous changes in membrane potential of the gastrointestinal smooth muscle that controls the timing of contractions.

**electrical response activity** Electrical activity of gastrointestinal smooth muscle associated with contractions.

**electrical slow waves** Phasic electrical activity underlying generation of spontaneous mechanical activity.

**electrochemical gradient** The driving force underlying the movement of charged compounds (or nonelectrolytes cotransported with charged compounds) across a membrane.

**electrogastrogram** The myoelectrical signal recorded with electrogastrography methods.

**electrogastrography** Methods for recording and analyzing gastric myoelectrical activity from electrodes positioned on the abdomen.

**electrohydraulic lithotripsy** The destruction of calculi (stones) by fragmentation using a shock wave sent transcutaneously via ultrasound transducers.

**electrolytes** Charged ions, such as sodium and chloride, that are part of the ionic composition of body fluids.

**embolectomy** The surgical removal of an embolus.

**embolism** The obstruction or occlusion of a blood vessel, caused by a mass such as an air bubble or clot.

**embolus** A foreign body that obstructs the flow of blood, such as air or fat.

**empyema** An accumulation of pus in a cavity of the body; can refer to accumulation external to or in the gallbladder.

**emulsions** Large lipid droplets.

**encapsulated organisms** Bacteria with a well-developed cell wall (e.g., pneumococcus).

**encephalopathy** Any of various diseases or degenerative conditions of the brain.

**encopresis** The voluntary or involuntary passage of a normal bowel movement in the underwear (or other unorthodox locations), after the age of 4 years, occurring on a regular basis without any organic cause.

**endocrine** Relating to the secretion of a hormone from a gland and transportation of the hormone in the bloodstream to a distant site, where the hormone exerts its action.

**endocytosis** The process by which a cell membrane folds inward to internalize substances.

**endoderm** One of the three germ layers formed by the process of gastrulation; this gives rise to the epithelial lining of the gastrointestinal tract and its derivatives.

**endodermal specification** The process by which the endoderm forms; distinct from the ectodermal and mesodermal layers of the early embryo.

**endolytic breath test** A breath test based on metabolism of a substrate labeled with isotopic carbon by tissue enzymes.

**endopeptidase** An enzyme that cleaves peptide bonds within a dietary protein that are adjacent to certain specific amino acids.

**endoplasmic reticulum (ER)** The membrane network in cytoplasm that is composed of tubules or cisternae. Some membranes carry ribosomes on their surfaces (rough endoplasmic reticulum) whereas others are smooth.

**endoscope** A medical instrument used to examine the inside of the stomach and duodenum; it consists of a thin, long, flexible tube that contains a light and camera, which can be easily passed through the mouth and into the stomach and duodenum. A small, flexible wirelike instrument can be inserted through the endoscope and out its end to sample or remove stomach masses such as polyps.

**endoscopic retrograde cholangiopancreaticography (ERCP)** A procedure in which a fiber-optic endoscope is inserted into the duodenum and dye is injected via the ampulla of Vater to visualize the biliary and pancreatic ducts. Certain interventional procedures can also be performed during ERCP, such as removal of stones, placement of stents, and tissue sampling.

**endoscopic ultrasonography (endoscopic ultrasound, endosonography)** A procedure utilizing an endoscope with an ultrasound probe mounted on the tip. This allows the physician to see beyond the endoscopic image provided by standard endoscopes. It is particularly useful for cancer staging.

**endoscopy** Visual inspection of any cavity of the body by means of an endoscope.

**end-stage liver disease** Signs and symptoms of a patient who has decompensated cirrhosis, e.g., ascites, encephalopathy, and esophageal variceal bleeding.

***Entamoeba dispar*** A morphologically identical commensal of *Entamoeba histolytica* that is not associated with disease, but may lead to incorrect diagnoses of amebiasis.

***Entamoeba histolytica*** The intestinal protozoan parasite that causes amebiasis.

**enteral** By way of the gastrointestinal tract.

**enteral formula** A nutrition product delivered via tube into the stomach or intestines. Usually, the formula is synthesized commercially from fixed ingredients. Rarely, the formula may consist of blenderized food.

**enteral nutrition (feeding)** The provision of nutrition and nutrients directly by tube into the gastrointestinal tract, bypassing normal eating mechanisms.

**enteric-coated** Describing oral medication that is coated or encapsulated to avoid acid damage in the stomach but dissolve in the intestine.

**enteric nervous system** The nerve cell bodies and their processes that are found in the wall of the gastrointestinal tract and that act to influence motor activity and other important gut functions. A largely autonomous system sometimes referred to as the "brain in the gut."

**enteritis** Infection with small intestine symptoms such as nausea, bloating, and abdominal pain, but without sigmoidoscopic changes; can follow ingestion of material contaminated with feces.

**enteritis necroticans** A severe necrotizing disease of the small intestine, associated with high mortality, caused by *Clostridium perfringens* type C; see also pigbel.

**enterochromaffin or enterochromaffin-like cells (ECL cells)** Specialized neuroendocrine cells in the gastric epithelium that control the peripheral regulation of acid secretion by releasing histamine as a paracrine stimulant.

**enterochromaffin-like cell carcinoid** A tumor of gastric ECL cells that usually does not metastasize, but can infiltrate into deeper layers of the gastric wall.

**enteroclysis** A type of radiographic examination of the small bowel.

**enterocytes** Mature absorptive cells that line the villi of the small intestine. These tall and columnar cells are highly differentiated to fulfill absorptive and secretory functions; they also form a barrier against penetration of bacteria and dietary antigens into the mucosa.

**enteroendocrine cell** A specialized epithelial cell diffusely distributed throughout the gut epithelieum that releases hormone after exposure to luminal contents and other stimuli.

**enterogastrone** A hormonal substance released in response to the presence of intestinal fats; it causes physiological inhibition of gastric acid secretion.

**enterohepatic circulation** The movement of bile from the gallbladder to the small intestine and from the small intestine to the hepatic portal vein, then on to the liver, where it is again secreted for storage in the gallbladder.

**enterokinase** The enzyme present on the brush border of small intestinal enterocytes that cleaves trypsinogen, producing trypsin.

**enteropathy** A disease of the small intestine.

**enteropathy-associated T-cell lymphoma (EATL)** A clinically aggressive tumor typically seen in patients with a long history of celiac disease.

**enterotoxin** A bacterial toxin that exerts its effect by stimulating net fluid secretion by intestinal epithelial cells, without damaging the cells; contrasts with other types of bacterial toxins, such as cytoskeletal-altering toxins, cytotoxins, and toxins with immune- or nerve-stimulating activity.

**epidermal growth factor (EGF)** A peptide that is tropic for the growth of epithelial cells in the gastrointestinal mucosa and elsewhere.

**epidural anesthesia** A technique in which local anesthetics are placed in the space around the spinal cord and its protective membrane, blocking nerve transmission.

**epigastric** Located in the central upper abdomen.

**epigenetic** Describing a genomic code other than the base pair code of the DNA sequence. The epigenetic code consists of DNA methylation and histone modifications. e.g., CpG DNA methylation.

**episcleritis** Inflammation of the sclera of the eye, sometimes occurring in patients with active ulcerative colitis.

**epithelial** Relating to or composed of epithelium.

**epithelial cell balance** The physiological process that controls the birth and death rates of cells to maintain the morphology and function of epithelia in organs of the body.

**epithelial polarity** The property of epithelial cell asymmetry. Epithelial cells sit at the interface between two compartments and the cells have different surface and cellular features along an imaginary axis drawn between the two compartments.

**epithelium (*pl.* epithelia)** The cellular covering of the external and internal organs of the body.

**ergonomics** Design of environment or equipment related to natural body position and physical comfort.

**ergonovine** A drug that constricts blood vessels, used in provocative tests for sensitivity of smaller blood vessels in the heart to cause chest pain.

**erosion** A shallow ulcer or other defect confined to the mucosal layer.

**erythema nodosum** A disorder characterized by tender red bumps, usually found on the front of the lower leg; may occur in patients with active ulcerative colitis.

**esophageal stricture** A narrowing of the esophageal lumen.

**esophageal varices** Dilated blood vessels around the esophagus.

**esophageal web** A membrane obstructing the esophageal lumen.

**esophagectomy** Removal of the esophagus.

**esophagogastroduodenoscopy** Endoscopic examination of the esophagus, stomach, and duodenum.

**esophagojejunostomy** Surgical creation of an artificial passage between the esophagus and jejunum; the passage is used to reconstruct the intestinal tract following a total gastrectomy.

**esophagoscopy** Inspection of the interior of the digestive tract connecting the mouth and stomach with an endoscope.

**estimated energy requirement** The nutritional requirement for energy for individuals of normal weight with body mass indices of between 18.5 and 25 for adults.

**exchanger** An ion transporter that transports ions in opposite directions across the cell membrane.

**excretory ducts** Large ducts in the salivary glands running in the interlobular connective tissue and conveying saliva to the mouth.

**excystation** The emergence of trophozoites from cysts.

**exocrine pancreas** The portion of the pancreas that synthesizes and secretes the components of pancreatic juice. The juice contains digestive enzymes, water, and bicarbonate. The pancreatic acinar and ductal cells

constitute the cellular components of the exocrine pancreas.

**exocytosis** The process by which membrane-enclosed intracellular vesicles fuse with the plasma membrane and then open and release their contents to the extracellular space.

**exopeptidase** An enzyme that removes a single amino acid from the carboxyl-terminal of a dietary peptide or protein.

**external anal sphincter** Rings of skeletal muscle that surround the distal rectum and anal canal; respond to volitional commands to maintain continence when feces have moved into the rectum.

**extracellular matrix (ECM)** A complex array of macromolecules serving as the support or scaffolding for cells, and also regulating cellular functions to some degree.

**extracolonic** Pertaining to areas outside the colon itself.

**extraintestinal manifestations** A term for areas with disease involvement outside of the intestinal tract in patients with Crohn's disease. They can affect any organ, mucosal, or epithelial surface.

## F

**false aneurysm (pseudoaneurysm)** A type of aneurysm that involves a disruption of the arterial wall with containment by surrounding tissue or hematoma.

**familial adenomatous polyposis (FAP)** An inherited syndrome in which thousands of polyps develop in the colon, as well as in the stomach and upper intestine (duodenum). Bony tumors, known as osteomas, and other soft tissue tumors can also occur (Gardner's variant).

**familial polyposis coli** A general neoplastic disorder of the intestine, presenting most commonly as multiple polyps in the colon.

**Fanconi's syndrome** A disorder of the proximal kidney tubules characterized by urinary excretion of large amounts of amino acids, glucose, and phosphate despite normal blood levels of these molecules.

**fecalith** A small hard mass of feces.

**fecal-oral transmission** The acquisition of an infection by ingestion of fecally contaminated material that contains the infectious agent.

**fed motor pattern** The stereotypic contractile pattern that initiates soon after a caloric meal and that is responsible for mixing and propulsion of food residue for efficient digestion and absorption.

**fenestration** An opening in the surface of a structure, as in a membrane.

**ferritin** A mainly cytosolic molecule that binds excess iron, in both enterocytes and the liver. Ferritin complexes have the capacity to bind approximately 4500 iron molecules.

**ferroportin 1** A protein located on the basolateral surface of villous enterocytes; it functions as an exporter of iron from the enterocyte to the plasma; a mutation in ferroportin 1 is associated with an autosomal dominant form of iron overload in hereditary hemochromatosis type 4.

**fiber** See DIETARY FIBER

**fibrin-ring granuloma** A tissue mass with a central cavity surrounded by a ring of fibrin and epitheloid macrophages.

**fibroblast growth factors (FGFs)** Proteins expressed by the cardiac mesoderm; extracellular signals for inducing liver progenitor cells.

**fibrolamellar hepatocellular carcinoma** A tumor that is considered a histological variant of hepatocellular carcinoma, but with distinctive histological and clinical features.

**fibromyalgia** A disorder of pain and tenderness of muscle and adjacent connective tissue. Also known as **fibrositis** and **fibromyositis.**

**fibrosis** The end result of an inflammatory response of an organ or tissue to an irritation or injury, resulting in scar formation.

**filopodia** Narrow spike-like extensions of cell borders in cells that are not necessarily migrating.

**fissure** A painful split in the mucous membrane of the anus.

**fistula** An abnormal passage or connection between two or more epithelial-lined organs or between an epithelial-lined organ and the surface of the body.

**flatulence** The passage of colonic gas from the rectum.

**flavinoid** A collective term for a variety of polycyclic compounds that are present in vegetables, especially soy products. Many of the molecules have antiestrogen properties (these are termed "phytoestrogens").

**fluoroscopy** Examination by means of a fluoroscope, which is an X-ray device used for examining deep portions of the body.

**focal adhesions** Concentrated patches of stress fibers, associated proteins, and integrin receptors on the plasma membrane by which integrins attach to the extracellular matrix.

**food-borne illness (disease)** Any of various diseases, usually either infectious or toxic in nature, caused by agents that enter the body through the ingestion of food.

**food-borne pathogen** A microorganism that contaminates food intended for human consumption; *Campylobacter*, *Salmonella*, and *Shigella* are the most frequently implicated bacteria involved in food-borne illnesses.

**food intolerance** An abnormal physiologic response to an ingested food or food additive; intolerance has not been proved to be immunologic in nature and falls under the umbrella term, adverse food reaction.

**forkhead-related proteins** A family of transcription factors structurally similar to the product of the *Drosophila forkhead* gene. Also known as "winged helix" factors because of their three-dimensional structure. In mice and humans, the family has multiple members. It is now systematically known as the Fox family.

**foveolae** An opening of the gastric unit into the lumen of the stomach.

**free radical** 1. An uncharged atom or group of atoms having at least one unpaired electron, which makes it highly reactive. 2. An organic compound having some unpaired valence electrons; a normal by-product of oxidation reactions in metabolism.

**fulminant liver failure** Acute hepatitis occurring within 2–8 weeks of the onset of illness in the absence of preexisting liver disease, complicated by hepatic encephalopathy, massive hepatic necrosis, and a prolonged prothrombin time.

**functional** Affecting function but not structure; in some cases, this refers to the absence of a specific disease entity although there is a symptom.

**functional abdominal pain** The most common cause of recurrent abdominal pain in children (unknown etiology); no specific structural, infectious, inflammatory, or biochemical cause for the abdominal pain can be determined.

**functional dyspepsia** Dyspeptic symptoms with no definable organic cause; diagnosis is based on negative findings after evaluation of medical history, physical examination, blood tests, and upper endoscopy.

**functional gastrointestinal disease (disorder)** A collection of persistent or recurrent gastrointestinal symptoms that are present in the absence of any observable organic or physical abnormalities; symptoms include abdominal pain, bloating, early satiety, and urgency of defecation.

**fundoplication** A surgical procedure for the treatment of gastroesophageal reflux disease that involves strengthening the lower esophageal sphincter by wrapping the stomach fundus around it.

**fundus** The proximal portion of the stomach.

**fungistatic antifungal** A drug that inhibits fungal growth but does not kill fungi.

**fungitoxic antifungal** A drug that kills fungi.

**fusiform** Spindle-shaped.

## G

**gadolinium chelate** A magnetic resonance imaging intravenous contrast agent consisting of a complex of an organic ligand and a lanthanide metal.

**gallbladder** An organ of the biliary system that serves the functions of storing and concentrating bile. When the gallbladder is stimulated, such as following a meal, its contents are emptied into the biliary system and subsequently flow into the gut to enhance the digestive process. However, many animals lack gallbladders and humans usually have no symptoms after removal of the gallbladder.

**gallstone pancreatitis** Inflammation due to a gallstone obstructing pancreatic outflow.

**gallstones** Concretions formed in the biliary tract; composed of molecules that are insoluble in water, usually cholesterol and/or calcium bilirubinate.

**gamma camera** A device capable of detecting and localizing gamma rays, forming an image of the underlying radiopharmaceutical distribution within a patient. Most gamma cameras are capable of producing both planar and tomographic images.

**ganglia** Clusters of nerve cell bodies outside the central nervous system.

**gastrectomy** A surgical procedure in which part (i.e., a "partial" gastrectomy) or all (i.e., a "total" gastrectomy) of the stomach is removed.

**gastric** Pertaining to, affecting, or originating in the stomach.

**gastric accommodation** Relaxation of the proximal stomach to "accommodate" food without a major increase in intragastric pressure.

**gastric bypass** An operative procedure performed for the treatment of morbid obesity; the stomach is divided proximally into a small gastric pouch, which is drained into a Roux-en-Y jejunal limb.

**gastric dysrhythmia** Abnormal gastric myoelectrical rhythm (e.g., tachygastria).

**gastric emptying** The process by which ingested material is passed in a controlled fashion into the duodenum, where it undergoes further mixing and propulsion.

**gastric esophageal reflux disease** See GASTROESOPHAGEAL REFLUX DISEASE.

**gastric $H^+$,$K^+$-ATPase** An ATP-hydrolyzing enzyme responsible for catalyzing the exchange of lumenal $K^+$ for cytoplasmic $H^+$ by parietal cells, bringing about gastric lumenal acidification.

**gastric metaplasia** Mucus-type gastric cell growth that replaces the normal villous surface of the duodenal mucosa.

**gastric outlet obstruction** Near-complete or complete blockage of the pyloric channel connecting the stomach to the duodenum, manifesting as early satiety and vomiting of undigested food in adults and projectile, nonbilious vomiting in children.

**gastric polyp** A benign or malignant lesion in the stomach that is elevated above the surrounding gastric mucosa.

**gastric tachyarrhythmia** Abnormal dysrhythmic gastric activity that occurs at a frequency of 4–9 cycles per minute and that is often accompanied by reports of nausea.

**gastric varices** Dilated gastric veins that occur as a result of portal hypertension; may also occur as a result of splenic vein thrombosis.

**gastric volvulus** A condition in which the stomach twists upon itself.

**gastrin** A gastrointestinal polypeptide hormone produced by G cells of the gastric antrum; it stimulates gastric acid secretion.

**gastrinoma** A neuroendocrine tumor found mainly in the wall of the duodenum and in the pancreas; secretes excessive amounts of gastrin.

**gastrin-releasing peptide** A 27-amino-acid mammalian peptide that is closely related to bombesin and that was isolated from porcine stomach.

**gastritis** An inflammatory condition of the stomach, acute or chronic, that is sometimes due to an infectious pathogen.

**gastrocolic reflex** A change in the motility of the large intestine following ingestion of a meal.

**gastroduodenostomy** A type of gastroenterostomy in which a portion of the stomach is connected to the duodenum.

**gastroenteritis** A diarrheal process that affects the upper gastrointestinal tract and presents most typically as an acute watery diarrhea. Gastroenteritis usually denotes an acute diarrhea that is infectious and self-limiting.

**gastroenterostomy** The surgical creation of an artificial passage between the stomach and any part of the small intestine (e.g., the duodenum or jejunum).

**gastroesophageal reflux** The backflow of acidic stomach contents into the esophagus.

**gastroesophageal reflux disease (GERD)** A clinical syndrome that includes a variety of symptoms and tissue injury associated with abnormal exposure of the esophagus to regurgitated gastric (stomach) contents. Long-term complications of GERD can consist of erosion ulcers, stricture, Barrett's metaplasia, and esophageal adenocarcinoma. In children, gastroesophageal reflux disease is a significant entity in the differential diagnosis of pyloric stenosis.

**gastrointestinal motility** The process of contraction of the gastrointestinal wall that results in movement of food and secretions along the length of the gastrointestinal tract.

**gastrointestinal sphincter** A ring of circular muscle that contracts continuously and closes the lumen of the alimentary canal.

**gastrointestinal stromal tumors** Mesenchymal neoplasms that can be found throughout the digestive tract.

**gastrointestinal tract** A collective term for the portion of the body comprising the pharynx, esophagus, stomach, small bowel, colon, and rectum.

**gastrointestinal tract contrast examination** Radiographic examination of the gastrointestinal tract utilizing a radiopaque substance to facilitate visualization of portions of the gastrointestinal tract.

**gastrojejunostomy** The surgical creation of an artificial passage between the stomach and the jejunum.

**gastroparesis** A chronic condition characterized by delayed emptying of the stomach (in the absence of an obstruction), resulting in gastric retention of ingested material; may be idiopathic or due to drugs or an underlying condition, such as diabetes mellitus.

**gastropathy** A disorder of the stomach that includes gastritis and other noninflammatory conditions.

**gastroplasty** A surgical procedure in which the stomach is reshaped, reconfigured, or reconstructed with sutures or surgical staples.

**gastrostomy** An artificial opening in the stomach wall, usually created by surgical means.

**gastrostomy tube** A flexible, rubberlike tube that is inserted through a gastrostomy into the stomach.

**gemcitabine** A chemotherapeutic agent and potent radiosensitizer that has recently been added to the multimodality treatment regimen for pancreatic adenocarcinoma.

**gene promoter** A noncoding DNA sequence of a gene at which RNA polymerase and transcription factors bind and regulate transcription.

**genetic counselor** A professional with master's-level training in medical genetics, counseling, and the psychosocial/legal issues associated with inherited disorders and genetic testing.

**genetic heterogeneity** A condition in which several different mutations in the same gene are found in a genetic disorder.

**genetic polymorphism** A variant in the genetic material that codes for a specific biological protein (such as for a neurochemical receptor on the surface of neurons).

**genetic testing** An analysis of chromosomes, genes, and/or gene products (e.g., proteins or enzymes) to determine whether a genetic alteration related to a specific disease or condition is present in an individual.

**genomic instability** Loss of fidelity of DNA in cells, resulting in changes to the genomic DNA code.

**genotype** The genetic constitution of an individual.

**geophagia** The practice or habit of eating clay or earth.

**GERD** See GASTROESOPHAGEAL REFLUX DISEASE.

**germ-line mutations** Genetic alterations that occur in the cells that are of direct descent, from the zygote to gamete; these are transmitted to progeny.

**giant migrating contraction** A large-amplitude, long-duration, lumen-occluding contraction that rapidly propagates over long distances. It causes mass movement and produces descending inhibition of contractions and relaxation of tone to facilitate rapid propulsion.

**Gibbs-Donnan equilibrium** Distribution of anions and cations when an impermeable anion is present on one side of the membrane. Electrostatic effects lead to enrichment of divalent cations on the side of the impermeable anion. In bile, this results in the concentration (activity) of $Ca^{2+}$ ions being higher in gallbladder bile than in plasma.

**Gilbert's syndrome** Genetic polymorphism resulting in impaired bilirubin conjugation.

**gliadin** The alcohol-soluble protein fraction of gluten.

**Glisson's capsule** The external capsule of the liver.

**globus** The sensation of a lump or some object or mass stuck in the throat, tightness of the throat, or inability to swallow.

**glomerulonephritis** Inflammation of the renal glomerulus often due to infectious or immune disorders; red blood cells, and red and white blood cell casts commonly seen on urinalysis.

**glottis** The opening in the larynx through which exchange of air occurs between the mouth and lungs.

**glucagon** A hormone produced by alpha cells in the islets of Langerhans; acts to elevate blood glucose.

**gluconeogenesis** The formation of new glucose from noncarbohydrate substrates, including various amino acids, lactate, pyruvate, and glycerol.

**glutathione** A tripeptide consisting of glutamic acid, cysteine, and glycine. The sulfhydryl group on the cysteine is used for conjugation of a number of organic anions, especially those containing halogen groups.

**gluten** The water-insoluble protein-rich residue remaining after wheat starch has been extracted from the dough made from wheat flour; can be responsible for damage of the small intestine in celiac disease.

**glycogen** A complex, hydrated polymer of glucose with a very large molecular weight (ranging over several million Daltons), consisting of many glucose molecules joined together to form a compact, highly branched spherical structure with a large number of exposed terminal glucose molecules that are accessible to the enzymes involved in glycogen breakdown (glycogenolysis).

**glycogen storage diseases (glycogenoses)** Any of various inherited diseases caused by abnormalities of the enzymes that regulate glycogen synthesis and degradation.

**glycogenolysis** The intracellular breakdown of glycogen to glucose.

**glycolysis** The sequential enzymatic conversion of glucose to lactic acid.

**glycosidic linkage** A covalent chemical bond between the monosaccharide units of disaccharides, oligosaccharides, and polysaccharides formed by the removal of a molecule of water.

**goblet cells** Mucus-synthesizing and secreting cells found in the epithelium of pancreatic ducts.

**Golgi complex** The compartment of the cell responsible for maturation of lipoprotein particles prior to their secretion into the plasma.

**G-protein** A heterotrimeric guanine nucleotide-binding protein.

**G-protein-coupled receptors (GPCRs)** A family of cell surface receptor proteins consisting of seven transmembrane regions. The intracellular region interacts with guanosine triphosphate-binding proteins that, on ligand binding, transduce signals within the cell, leading to a cellular response (e.g., secretion, motility, and growth).

**gracilis muscle** A muscle located on the inner aspect of the thigh; it may be cut at its distal end and transposed around the anal canal to substitute for a damaged or denervated external anal sphincter. The transposed muscle is often electrically stimulated to maintain a state of contraction.

**gram-negative** A characteristic of bacteria that do not retain the violet stain used in Gram's method and therefore appear pink instead of blue after being stained.

**granular cell tumors** Generally benign growths that are derived from smooth muscle or Schwann cells.

**granuloma** Focal nodular accumulation of histiocytes in tissue

**growth factors** A class of proteins, usually secreted from cells, that exert their biological activity by binding to high-affinity, cell surface receptors at low concentrations; most growth factors have diverse biological activities including actions independent of cell growth regulation.

**guanylin/uroguanylin** Small peptide hormones produced in the intestine, where they act locally to regulate intestinal functions, including the secretion of electrolytes and fluid into the intestinal lumen.

**gustatory** Relating to taste.

**gut manometry** The evaluation of gut motility by measuring intraluminal pressures.

**gut tone** Tonic, i.e., sustained, muscular contraction of the gut wall.

**gynecomastia** The excessive development of the male mammary glands.

## H

**halitosis** Bad breath; abnormally foul or fetid breath.

**hamartoma** Mature but disorganized normal tissue indigenous to the site of origin.

**hamartomatous polyp** A benign polyp that arises from the overgrowth of some constituent of the lamina propria, submucosa, or muscular tissue. Some conditions with hamartomatous polyps have a malignant predisposition.

**Hamman sign** A mediastinal crunching sound with heartbeat.

**haptocorrin** A cobalamin-binding glycoprotein of unknown function produced by the salivary glands, stomach, and other foregut tissues of mammals.

**health-related quality of life** A term for the impact that illness has on quality of life, including the individual's perception of his or her illness.

**heartburn** A specific symptom of gastroesophageal reflux disease, typically manifested by a burning sensation in the upper abdomen, behind the chest, and as high as the throat.

**helical computed tomography (CT)** CT technology that acquires a volume of data rather than acquiring data slice by slice as in older technology.

***Helicobacter pylori*** A gram-negative urease-producing bacterium that causes an active chronic gastritis and is an important etiological factor in the development of gastric and duodenal ulcers.

**HELLP syndrome** A triad of hemolysis, elevated liver tests, and low platelet count in the third trimester of pregnancy.

**helminth** A general term for a parasitic worm.

**hemagglutinin** The viral protein that binds to erythrocytes.

**hemangioma** A vascular tumor that can be found in the small intestine and colon; considered the second most common vascular lesion of the colon (after angiodysplasia). Hemangiomas can be classified into two distinct types, capillary hemangiomas and cavernous hemangiomas. They can become very large and present with gastrointestinal bleeding.

**hematemesis** The vomiting of blood; indicates an upper gastrointestinal site of bleeding.

**hematochezia** The passage of bright red or wine-colored stool, usually representing bleeding from the lower gastrointestinal tract, often the colon.

**hematochromatosis** A disorder of iron metabolism characterized by the excessive absorption of ingested iron.

**hematocrit** The percentage of the blood sample volume occupied by cells.

**hematogenous spread** Dissemination via the circulation.

**hematopoiesis** Creation of the formed elements of the blood (e.g., red corpuscles).

**heme** The oxygen-carrying portion of hemoglobin.

**hemobilia** Blood in the bile ducts, which then passes into the duodenum and is either vomited or passed per rectum.

**hemochromatosis** An inherited disease in which excessive accumulation of iron can affect the liver, heart, pancreas, and skin. Complications of liver involvement include cirrhosis and hepatocellular carcinoma.

**hemolysis** The destruction of red blood cells with concomitant release of hemoglobin.

**hemolytic uremic syndrome** A sequela of *Escherichia coli* O157:H7 colitis. This toxin-mediated microangiopathy results in a triad of hemolytic anemia, thrombocytopenia, and renal failure. The occurrence of the syndrome is generally limited to children under 10 years of age.

**hemorrhage** The loss of blood from blood vessels.

**hemorrhoids** Varicosities of the external hemorrhoidal veins that may result in a painful swelling at the anus and have a propensity for bleeding.

**hemostasis** The arrest or control of bleeding.

**hepatic** Relating to or involving the liver.

**hepatic artery chemoembolization** Ablative therapy in which the blood supply of a tumor is selectively decreased by embolization to cause tumor cell death. In addition to decreasing the blood supply, a chemotherapeutic agent can be applied directly to the tumor.

**hepatic cirrhosis** See CIRRHOSIS.

**hepatic encephalopathy** Altered mental status in a patient with end-stage liver disease, ranging from mild confusion to coma; stems from the fact that in a cirrhotic liver, the cells have been replaced with scar tissue and are no longer able to remove toxins from the blood.

**hepatic hydrothorax** Pleural effusion (more than 500 ml) in patients with cirrhosis, in the absence of cardiopulmonary or subdiaphragmatic pathology.

**hepatic venous pressure gradient** The gradient between the wedged, or occluded, hepatic venous pressure and free hepatic venous pressure; provides a reliable measurement of portal pressure.

**hepaticojejunostomy** A surgical procedure in which the common hepatic duct is connected to the jejunum.

**hepatitis** Inflammation of the liver. The process may be acute or chronic according to the level of exposure to the damaging agent.

**hepatitis B virus** A DNA virus that infects humans and is transmitted by blood, sex, or childbirth. Some chronically infected patients can progress to cirrhosis and hepatocellular carcinoma.

**hepatitis C virus** An RNA virus that infects humans and is transmitted primarily through blood. Most patients become chronically infected and some will develop cirrhosis and hepatocellular carcinoma.

**hepatitis D virus** A subviral human pathogen requiring helper functions of the hepatitis B virus to replicate and induce disease.

**hepatocellular carcinoma (hepatoma)** Liver cancer.

**hepatocytes** Individual cells constituting the liver.

**hepatojugular reflux** Sustained increase in jugular venous pressure elicited by compression of the abdomen in patients with right heart failure.

**hepatolithiasis (Oriental cholangiohepatitis)** A chronic disease characterized by the formation of primary intrahepatic pigmented stones and sequelae that include recurrent cholangitis, strictures of the intrahepatic bile ducts, hepatic abscesses, portal vein thrombosis, cholangiocarcinoma, and sometimes secondary biliary cirrhosis with hepatic failure.

**hepatomegaly** Increase in the size of the liver. In children, normal size varies with age.

**hepatorenal syndrome** Development of kidney failure in patients with acute or chronic liver failure in the absence of any other known cause of renal disease.

**hepatotoxicity** The fact or condition of toxic damage to the liver.

**hepcidin** A small protein produced by hepatocytes; may be the soluble iron stores regulator that controls iron absorption in intestinal crypt cells.

**hephaestin** A protein located on the basolateral surface of villous enterocytes; functions as a ferroxidase, converting ferrous ($Fe^{2+}$) to ferric ($Fe^{3+}$) iron, facilitating its transfer across the basolateral membrane of the enterocyte to the plasma.

**hereditary** Transferred via genes from parent to child.

**hereditary cancer syndrome** A collection of clinical features, including cancers, attributable to an alteration in a single gene that can be passed from parents to their children.

**hereditary hemochromatosis** A disorder of iron metabolism in which affected individuals absorb an excessive amount of iron that accumulates in internal organs and may eventually interfere with cellular function.

**hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease)** a disorder with autosomal dominant inheritance of vascular malformations in multiple organ systems, including the lungs, brain, and gastrointestinal tract.

**hereditary nonpolyposis colorectal cancer** An autosomal dominant condition in which there is an increased risk of developing colorectal cancer, as well as ovarian, renal, pancreatic, and endometrial cancers.

**hereditary pancreatitis** An autosomal dominant disease that accounts for 1% of cases of both chronic and recurrent pancreatitis; genetic mutations have been identified in cationic trypsinogen for many patients.

**heterozygote** An individual with two different alleles at a specific locus.

**hiatal hernia** Protrusion of part of the stomach, usually the cardia, into the thoracic cavity through the esophageal opening of the diaphragm.

**high-amplitude propagating contractions** Colonic contractions that produce mass movements when present in the transverse and ascending colon and defecation when present in the descending or sigmoid colon.

**high-density lipoproteins (HDLs)** Class of serum lipoproteins; like other lipoproteins, their core consists of neutral lipid surrounded by an envelope of polar lipid and specific proteins called apoproteins. High-density lipoproteins protect against atherosclerosis through a process known as reverse cholesterol transport, the pathway responsible for transporting excess cholesterol from the peripheral tissues back to the liver for excretion.

**highly active antiretroviral therapy** A combination of different anti-human immunodeficiency virus (HIV) drugs, usually including a protease inhibitor, that have markedly increased the prognosis for patients with HIV.

**high-resolution anoscopy** Technique similar to cervical colposcopy; uses identical equipment (a powerful light source and binocular lenses) to allow identification and biopsy of lesions that have contributed to abnormal anal cytologic findings.

**Hirschsprung's disease** A congenital disorder characterized by severe constipation due to absence of neurones in the myenteric plexus of the distal gut.

**histamine** A vasoactive amine, vasodilator, and smooth muscle constrictor that is found in high concentrations in mast cells.

**histamine-2 (H2) receptor antagonists** Drugs that block the action of histamine at a specific (type 2) histamine receptor located in the stomach, which results in effective inhibition of gastric acid secretion.

**holistic** Referring to therapies based on information about the "whole person," including spiritual, physical, mental, emotional, environmental, and social health.

**homeobox genes** Transcription factors that contain a homeobox or homeodomain, a conserved nucleotide sequence that encodes a DNA binding domain.

**homeobox/homeodomain** Specific sequences of transcription factor nucleotides and amino acids that confer a DNA binding patterning/regulation capacity.

**homeostasis** The ability of an organism to maintain an ongoing internal balance or equilibrium (i.e., a balance between cell loss and cell production); critical to survival and health.

**homocysteine** An amino acid that is converted to methionine with cobalamin as cofactor. Cobalamin deficiency leads to increased levels of homocysteine, which is used to diagnose cobalamin deficiency.

**hormone** In the classic sense, a chemical messenger that induces a specific response in target cells distant from the site of synthesis. Now often broadened to include local cell signaling as well; e.g., cytokines.

**human leukocyte antigen B27** A genetically determined self-antigen (protein) localized on tissue cell surfaces.

**human papillomavirus** A family of 60 subtypes of sexually transmitted viruses responsible for genital tract infections, such as condylomata (genital warts). Chronic infection with subtypes 16 and 18 has been identified as a strong risk factor for the development of cervical cancer and anal cancer.

**hydatid cyst** A cyst formed by the larval form of *Echinococcus*. Often appears as a "mother" cyst with several smaller "daughter" cysts.

**hydrocolosinography** Examination of the colon after it has been filled with fluid.

**hyperamylasemia** Abnormally high concentrations of the digestive enzyme amylase in the blood.

**hyperbilirubinemia** A condition in which an abnormally large amount of bilirubin circulates in the blood, resulting in serum total bilirubin concentrations greater than the 95$^{th}$ percentile for hour of life.

**hyperechoic** Ultrasound description of lesions that reflect sound waves.

**hyperemesis gravidarum** A pernicious condition in which the pregnant patient develops severe and intractable nausea and vomiting associated with nutritional and fluid/electrolyte deficiencies.

**hyperglycemia** The condition of having a higher than normal plasma glucose concentration. Normal values of plasma glucose differ depending upon the whether the subject is in the fasting or fed state.

**hypergonadotropic hypogonadism** Reduced function of the gonads (ovaries or testes) due to congenital failure of development or postnatal damage or destruction, associated with elevation of gonadotropin (pituitary hormone) levels.

**hyperlipidemia** An elevated concentration of plasma lipoproteins.

**hyperosmolar fluid** A highly concentrated solution that contains several osmotically active particles, such as glucose or sodium.

**hyperplasia** Increase of cell proliferation to a level that is higher than normal.

**hyperplastic polyp** A nonneoplastic epithelial polyp that is typically found in the colon. These tiny polyps account for approximately half of the polyps found in the colon and their primary importance is distinguishing them from adenomatous polyps.

**hypersplenism** A condition, usually associated with portal hypertension, in which the spleen is enlarged, sequestering platelets and red and white blood cells.

**hypertensive lower esophageal sphincter** A manometric finding of uncertain clinical significance; frequently found in patients with noncardiac chest pain or nonorganic dysphagia without detectable underlying cause.

**hyperthyroidism** A variety of disorders resulting in excessive thyroid hormone levels and effects throughout the body.

**hypertrophy** Growth characterized by an augmentation of cell volume.

**hypoalbuminemia** An abnormally low concentration of albumin in the blood.

**hypochlorhydria** The condition of having decreased amounts of stomach acid.

**hypoglycemia** A condition in which plasma glucose concentration is decreased sufficiently to produce symptoms, which improve with restoration of normal plasma glucose.

**hypokalemia** Abnormally low potassium concentrations in the blood.

**hypophosphatemia** Low blood phosphorus concentration.

**hypoplasia** Decrease of cell proliferation to a level that is lower than normal.

**hypoproteinemia** Abnormally small amounts of total protein in the blood.

**hypotension** Abnormally low blood pressure.

**hypothalamus** An integrative brain area made up of different nuclei; it receives inputs from the periphery and triggers the appropriate behavioral and biochemical responses.

**hypothermia** Body temperature significantly below normal.

**hypothyroidism** A syndrome characterized by inadequate thyroid hormone production or replacement.

**hypoxia** A condition that arises when the cellular demand for molecular oxygen necessary to maintain physiologic function exceeds supply.

## I

**IBD** See INFLAMMATORY BOWEL DISEASE.

**IBD1** The first gene locus identified in inflammatory bowel disease. It is located in the peri-centromeric region of chromosome 16 and contains the NOD2 gene.

**ileal brake** An endocrine mechanism, elicited by the presence of nutrients in the ileum, that causes inhibition of upper gastrointestinal secretion and/or motility.

**ileitis** Inflammation of the ileum.

**ileoanal pouch** A reservoir created from the distal ileum to connect the ileum to the anus after total colectomy.

**ileostomy** An operation in which, after removal of the colon (colectomy), the cut end of the ileum is brought through an opening in the abdominal wall. Ileal effluent is collected thereafter into a bag fixed over the stoma.

**ileus** The failure of downward progress of the intestinal contents because of disordered propulsive motility of the gastrointestinal tract.

**image resolution** The degree to which very small objects located in close proximity can be distinguished in an image.

**imaging device** Machinery that scans and captures body images (as in computed tomography, magnetic resonance imaging, radiography, and fluoroscopy).

**imaging plate** A system analogous to silver nitrate film, but using phosphorescent technology to capture images digitally, rather than converting silver to form an image.

**immune-enhancing formula** An enteral formula with added substrates (often arginine, fatty acids, ribonucleic acids, and glutamine). Such formulas are postulated to enhance intestinal immune function.

**immune reconstitution** Immune-specific responses that can be transiently associated with unusual manifestations of opportunistic infections, such as *Mycobacterium avium* complex lymphadenitis. This occurs several weeks to months after highly active antiretroviral therapy is initiated, as CD4 lymphocytes expand.

**immunodeficiency** Any condition in which the body's immune system (antibodies, T cells) is not functioning at optimal capacity.

**immunoglobulin (Ig)** A protein (antibody) produced by B cells; it has the ability to recognize and bind specific antigens. Types include immunoglobulin A, E, G, M; IgA is the dominant immunoglobulin of intestinal secretions and is found also in saliva and bile.

**immunoneutralization** A technique to abolish the effect of a circulating peptide by administering antibodies directed against the peptide.

**immunostain** A laboratory histochemical procedure that detects a specific antigen using a specific antibody.

**immunosuppression** Prevention or interference with the development of an immunologic response; it may reflect natural immunologic unresponsiveness (tolerance), may be artificially induced by chemical, biological, or physical agents, or may be caused by disease.

**imprinting** A germ-line process that "presets" or predetermines the potential of a transmitted gene to be active or inactive without changing the actual sequence of the base pairs. It presumably reflects a modification of the DNA or proteins in such a way as to preset the activity of genes in the embryo.

**incidence** The number of new cases of a specific disease found in a defined population over a specific time period (such as the number of new cases over a one-year period).

**incretin hormones** Insulinotropic intestinal hormones responsible for enhanced insulin secretion after oral as opposed to intravenous glucose administration.

**indeterminate colitis** Chronic idiopathic inflammatory colitis that cannot be classified with certainty as ulcerative colitis or Crohn's disease based on endoscopic, radiographic, and histopathologic criteria.

**inducible nitric oxide synthase** Key enzyme for production of nitric oxide, a potent endogenous vasodilator that acts through smooth muscle relaxation.

**INDY gene** A recently discovered "I'm not dead yet" gene locus, the mutation of which can slow senescence and extend longevity; encodes for a protein that down-regulates cellular energy utilization.

**inflammation** The body's response to infection or injury, including increased swelling, redness, heat, pain, and white cell infiltration (pus formation).

**inflammatory bowel disease** A group of chronic, idiopathic disorders characterized by inflammation of the gastrointestinal tract. The term most commonly refers to Crohn's disease (CD) and ulcerative colitis (UC).

**inflammatory diarrhea** A diarrheal illness in which the predominant pathologic finding is an invasion of the intestinal epithelium by immunocytes. This type of diarrhea can be the result of either a normal immune response to an abnormal environment, as in infection, or an abnormal immune response to a normal environment, as in inflammatory bowel disease.

**inflammatory polyp** A pseudo-polyp, consisting of normal tissue, often with increased inflammatory elements; mostly associated with chronic inflammatory conditions of the bowel including ulcerative colitis and Crohn's disease. They do not have malignancy risk, but the inflammatory conditions themselves do.

**infliximab** A humanized monoclonal antibody directed toward the tumor necrosis factor alpha (TNFα) that has shown great efficacy in the therapy of Crohn's disease.

**informed consent** Agreement and acknowledgment of understanding by the patient for a procedure or intervention following an explanation of the risks, benefits, and alternatives.

**initiation/elongation factors** A group of proteins involved in the initiation and synthesis of polypeptide chains at the level of translation.

**in-phase gradient echo** A magnetic resonance pulse sequence in which signals from lipid and water are additive.

**INR (International Normalized Ratio)** A test that measures clotting impairment.

**insufflation** Installation of air into the colon for the purpose of distending the walls for examination.

**insulin** A glucose-regulating hormone produced and secreted by beta cells in the islets of Langerhans; it has broad anabolic effects on body metabolism.

**insulinoma** An insulin-producing tumor of the pancreatic beta cells in the islets of Langerhans.

**insulin resistance** The decreased ability of insulin to act effectively on peripheral target tissues, especially muscle and liver; resistance is relative, because supernormal levels of circulating insulin will normalize the plasma glucose.

**insulin secretagogues** Drugs that improve insulin secretion: sulfonylurea and metiglinides.

**insulin sensitizers** Drugs that improve insulin action: biguanides (metformin) and thiazolidinediones (rosiglitazone and pioglitazone).

**intercalated ducts** Small ducts in salivary glands connecting the secretory cells to larger striated ducts.

**intercellular adhesion molecules** Molecules that assist leukocytes in interacting with their environments through adherence; they are changed on the surfaces of endothelial cells and leukocytes during inflammation and help recruit leukocytes to sites of inflammation.

**intercellular canaliculi** Finger-like projections of the endpiece lumen extending between adjacent secretory cells.

**interdigestive motility complex** See MIGRATING MOTOR COMPLEX

**interdigestive state** Physiologic conditions in the digestive tract in the time between completion of digestion and absorption of a meal and the ingestion of the next meal.

**interferons** A large family of naturally occurring peptides with both antiviral and antiproliferative effects.

**intermediate host** An animal, vertebrate or invertebrate, that serves as a host for an intermediate developmental stage of a parasite. The intermediate host transmits the parasite by releasing a form infectious to the definitive host or by being consumed by the definitive host.

**intermittent clamping** A strategy to prevent ischemic injury by interrupting long ischemic insults with multiple short intervals of reperfusion.

**internal anal sphincter** A ring of smooth muscle that surrounds the distal rectum and anal canal; it obstructs the passage of feces when contracted and permits passage when relaxed.

**internal hemorrhoids** Hemorrhoids that originate above the dentate line. Differentiated as first through fourth degree: first degree, slide below the dentate line on straining; second degree, prolapse through the anus on straining but reduce spontaneously; third degree, prolapse through the anus on straining and require manual replacement into the anal canal; fourth degree, prolapse is not manually reducible.

**internal intussusception** Rectal intussusception in which the lead point remains above the pelvic floor (also called occult prolapse).

**internal ribosome entry site** An intricate RNA structure that is located near the beginning of hepatitis C virus RNA; it promotes the initiation of viral protein synthesis.

**interneurons** Neurons that relay signals among ganglia in a three-dimensional structure.

**interstitial cells of Cajal** Specialized cells that are located at the interface of the longitudinal and circular muscle layers of the gut wall and that generate rhythmic electrical depolarizations (slow waves) acting as pacemakers for duodenal contractions.

**intestinal absorption** The capacity of the intestinal mucosa to actively absorb digested food.

**intestinal failure** An irreversible state of inability of the native gastrointestinal tract to provide for the nutritional and/or fluid and electrolyte demands of the body.

**intestinal infarction** Loss of viability of any portion of the bowel due to the lack of sufficient blood supply to ensure adequate perfusion over a significant period of time.

**intestinal intrinsic nervous system** A complex system of interconnecting nerve fascicles and ganglia occurring within the intestinal wall and able to function autonomously.

**intestinal lengthening** A surgical procedure in which the dilated small intestinal diameter is halved and joined end to end.

**intestinal metaplasia** A condition in which the intestinal cells in the gastric mucosa become metaplastic.

**intestinal permeability** Property of the intestinal mucosa to permit the passage (diffusion) of substances across the mucosa.

**intestinal pseudo-obstruction** Clinical symptoms, either recurrent or chronic, resembling a mechanical obstruction of the gut without demonstrable luminal compromise.

**intestine-kidney endocrine axis** Hormonal connection between the intestine and kidney formed by enteric guanylin and/or uroguanylin peptides that are secreted into the bloodstream following the ingestion of dietary sodium chloride (i.e., table salt).

**intraepithelial lymphocyte compartment** Collection of T lymphocytes and NK (natural killer) cells interspersed between the intestinal epithelial cells.

**intrahepatic cholestasis of pregnancy** Pruritus and liver dysfunction in the second half of pregnancy.

**intraluminal contrast** A dilute solution (2%) of barium or Gastrografin™ that is ingested to distend and opacify the hollow abdominal viscera. This is helpful in differentiating the gut from masses, lymph nodes, and abscesses.

**intravascular contrast** A process in which iodinated contrast material is injected into an antecubital fossa vein to assess bowel wall enhancement, to identify and characterize focal lesions in the liver, spleen, pancreas, adrenal glands, kidneys, and bladder, and to perform computed tomography-angiography.

**intravillous space** The space between the long villi. Nutrients must diffuse into this space in order to be taken across the brush border membrane in portions of the villus away from the villus tip and toward the crypt.

**intrinsic factor** A glycoprotein secreted by the stomach; it binds cobalamin specifically, attaches to a receptor (cubilin) on the apical membrane of the ileal epithelial cell, and is internalized together with its cobalamin by that cell.

**intubation** The process of obtaining access to the gastrointestinal tract with a tube.

**intussuscepiens** The intestinal loop, or sheath, into which the intussusepting bowel (the intussusceptum) invaginates.

**intussusception** The telescoping or invagination of one portion of the bowel into the adjacent, distal intestinal lumen.

**intussusceptum** Invaginating and returning bowel of the intussusception, including the adjacent mesentery.

**ion channel** A membrane protein that forms a selective and regulated pore for the diffusion of a particular ion or ions. The direction of movement is dependent on the electrochemical driving force for the given ion, which is determined by the concentration of ion on each side of the membrane and the electrical potential across the membrane.

**ion exchangers** A subclass of cotransporters that move substances in opposite directions; antiporters.

**ionizing radiation** Energetic particles, emitted by some isotopes of certain atoms, that interact with biological tissues to cause ionization, leading to chemical, structural, or physiological changes in cells.

**ion pump** A membrane protein in which ATP hydrolysis is used as an energy source to move one or more ions across the cell membrane.

**ions** Elements that have a positive (cationic) or negative (anionic) charge due to the loss or gain of one or more electrons.

**IPEX syndrome** immunodysregulation, polyendocrinopathy, and enteropathy: X-linked; an inherited X-linked syndrome that results from a mutation in the FOXP3 gene in humans. It is characterized by autoimmune enteropathy and multiple endocrinological abnormalities including diabetes mellitus, hypothyroidism, and hemolytic anemia.

**iron-responsive elements (IREs)/iron-regulatory proteins (IRPs)** Molecules that participate in the regulation of expression of some genes involved in iron absorption. IRPs bind to IREs and increase or decrease the expression of specific genes.

**irritable bowel syndrome** A group of functional gastrointestinal disorders seen frequently by gastroenterologists; patients have chronic and recurrent gastrointestinal symptoms such as abdominal pain, bloating, diarrhea, and constipation. Because there is no evident physical or biochemical basis, the syndrome is thought to be due to altered sensory or motor regulation of the gastrointestinal tract.

**ischemia** A decrease in the blood supply to an organ, tissue, or body part caused by constriction or obstruction of a vessel.

**ischemic** Describing an inadequate supply of blood to a part of the body, caused by partial or total blockage of an artery.

**ischemic preconditioning** A regimen used to prime an organ against subsequent long ischemic insults; it consists of a short period of ischemia followed by a brief interval of reperfusion prior to the prolonged ischemic insult.

**islet-acinar portal system** A specialized vascular system connecting the islets of Langerhans and the exocrine pancreas that delivers islet hormones to the acinar cells.

**islets of Langerhans** Clusters of several hundred to several thousand endocrine cells embedded in the pancreas.

**isoenzymes** Multiple forms of the same enzyme; they have subtle differences in amino acid sequence or posttranslational modifications.

**isolated intestinal transplant** Vascularized transplantation of the jejuno-ileum from another person (usually a cadaver).

**isotonic fluid** A solution that contains electrolytes, nonelectrolytes, or a combination of both, having the same concentration as the solution to which it is being compared (e.g., blood).

## J

**Janeway lesion** Painless, macular lesions on the palms and soles, characteristic of infective endocarditis.

**jaundice** Excessive accumulation of bilirubin, as a result of enhanced production or impaired elimination, resulting in yellow discoloration of the skin, sclera, and mucous membranes.

**jejunum** The second portion of the small intestine, which immediately follows the duodenum.

**Jennerian** Referring to vaccines, the use of naturally attenuated but antigenically similar animal strains as human vaccines, as Edward Jenner used cowpox virus to protect against smallpox.

## K

**Kaposiform hemangioendothelioma** Endothelial hyperplasia, which is less discrete and more aggressive than typical hemangioma. It can be associated with very low platelet counts (known as Kasabach-Merritt phenomenon).

**Kawasaki syndrome** Vasculitis; this has replaced rheumatic fever as the most common cause of acquired heart disease in children and is diagnosed on the basis of fever plus other five criteria.

**keratoconjunctivitis sicca** Dry eye and associated symptoms due to the absence of the aqueous component of tears.

**kernicterus** A severe neurological condition associated with yellow staining and degenerative lesions of the basal ganglia of the brain of severely jaundiced term newborns or moderately hyperbilirubinemic premature neonates.

**kinase** An enzyme that catalyzes the transfer of phosphate from ATP to substrates.

**Kit** Type III tyrosine kinase receptor expressed on populations of interstitial cells of Cajal throughout the gastrointestinal tract.

**kock pouch (continent ileostomy)** A reservoir constructed, following colectomy, from approximately 40cm of ileum much like a pelvic pouch, but with the modification of a one-way nipple valve accessed by intubation directly through the anterior abdominal wall.

**K-ras** An oncogene; the mutated form is found in over 90% of pancreatic cancers.

**Kupffer cell** A hepatic macrophage that presents in the lumen of hepatic sinusoids.

**kwashiorkor** A protein deficiency state with adequate caloric intake, due to a moderate to severe systemic inflammatory response with some degree of accompanying semistarvation. Also known as protein malnutrition.

**kyphoscoliosis** Backward and lateral curvature of the spine.

## L

**lacrimal glands** The glands producing tear fluids that bathe the surface of the eye (cornea).

**lactase deficiency** Very low or absent lactase activity; determined by assay of an intestinal biopsy sample.

**Ladd's bands** Peritoneal attachments to an abnormally positioned cecum. They can cause obstruction of the duodenum by extrinsic compression.

**lamellipodia** Wide wave-like extensions of the cell border in migrating cells.

**lamina propria** The connective tissue compartment located between the epithelium and the muscularis, consisting of interstitial matrix as well as various cell types (fibroblasts and immune cells).

**lamina propria lymphocyte compartment** A collection of bone marrow-derived cells (including lymphocytes and antigen-presenting cells) dispersed throughout the stroma, supporting the intestinal villi.

**laparoscopic cholecystectomy** Removal of the gallbladder via a laparoscopic approach.

**laparoscopic staging** A minimally invasive means of evaluating the resectability of pancreatic adenocarcinoma by visualization through a tube inserted into the abdomen.

**laparoscopic surgery** The use of laparoscopy to perform diagnostic and therapeutic procedures in the abdominal cavity.

**laparoscopy** Visual inspection of the abdominal cavity via an endoscope or telescope, most often utilizing video monitoring via attachment of a camera to the endoscope.

**laparotomy** Surgical incision through the abdominal wall.

**larva** The immature form of an invertebrate that requires molting to develop to adult stage.

**larynx** The organ for production of voice; situated in the airway at the base of the tongue.

**latent celiac disease** Celiac disease in patients who have a normal small intestinal biopsy on a gluten-containing diet, but at some time before or since have an enteropathy that resolved with gluten restriction.

**lateral inhibition** A process by which a single, centrally located cell self-determines its differentiation and, in doing so, inhibits a similar fate selection by adjacent lateral cells.

**laxative** Any substance that acts to induce defecation and thereby increase stool frequency, soften stools, and ease the passage of stools.

**L cell** The endocrine cell type in the intestinal mucosa that expresses the glucagon gene and secretes the proglucagon-derived peptides.

**lean body mass** The fat-free compartment of the body, which contains nitrogen and makes up approximately 75% of body mass or weight. It includes the body cell mass, the extracellular fluid compartment, and the supporting tissues.

**lecithin cholesterol acyltransferase** An enzyme involved in the esterification of free cholesterol present in circulating plasma lipoproteins; a major determinant of the circulating level of high-density lipoproteins (for instance, overexpression of this enzyme in animals significantly increases the circulating plasma high-density lipoprotein levels).

**leptin** An adipocyte peptide hormone that serves to decrease appetite.

**Leser-Trelat sign** The sudden appearance of multiple seborrheic keratoses, often concomitant with acanthosis nigricans; found in association with gastrointestinal malignancies.

**leukopenia** A low white blood cell count.

**leukoplakia** A thick white patch on mucous membrane.

**leukotriene** Fatty acid product of arachidonic acid that contributes to the proinflammatory response.

**levator ani muscle** Part of the pelvic floor situated anterior to the anal canal; it can be voluntarily contracted to pinch off the rectum from the anal canal.

**life expectancy** The expected life span of an individual; can be defined as the predicted number of years that will pass until only half of any cohort of people will still be alive.

**ligament of Treitz** A suspensory muscle of the duodenum that anatomically divides the duodenum from the jejunum.

**ligand** A structure on one cell recognized by a receptor on another cell.

**lineage selection** The process by which developmental fate choices are made during organogenesis between different cell lineage types.

**lipase** An enzyme that catalyzes the hydrolysis of ester bonds in dietary fats to release fatty acids.

**lipid** A concentrated form of energy, composed of a number of classes of compounds that are insoluble in water but soluble in organic solvents; triacylglycerols and triglycerides are the most abundant of all dietary lipids.

**lipid absorption** The process by which lipids are digested, mainly in the intestinal lumen, where they are absorbed by enterocytes and then packaged and secreted as chylomicrons into the lymph. Bile salt plays a critical role in the absorption.

**lipid-binding proteins** Proteins in the brush border membrane and the enterocyte cytosol that bind lipids. Their physiological role is unknown; they may influence or modify intestinal absorption, bind lipids as they move from the brush border membrane to microsomes, or possibly play a role in the handling of adaptation.

**lipid rafts** Plasma membrane microdomains enriched with cholesterol and glycosphingolipids; serve as entry routes for bacterial toxins in target cells.

**lipogranuloma** Tissue mass containing lipid vacuoles surrounded by macrophages, lymphocytes, and collagen fibers.

**lipomas** Rare benign tumors of adipocytes that can occur throughout the gastrointestinal tract from the esophagus to the rectum.

**lipopolysaccharide** A lipid component of the cell wall of gram-negative bacteria.

**lipoprotein receptor** A class of receptors demonstrating affinities for certain lipoproteins. Some, such as the low-density lipoprotein receptor, cluster in coated pits and participate in the regulation of cholesterol homeostasis. Others, such as scavenger receptor type B1 and the ABC-type transporters ABC-A1, ABC-G5, and ABC-G8, play a role in cholesterol secretion and/or uptake that is not fully understood.

**lipoproteins** Particles carrying lipids in blood. Lipoproteins consist of esterified or unesterified cholesterol, triglycerides, phospholipids, and protein.

**lipoprotein X** An abnormal lipoprotein that is rich in free cholesterol and phospholipids. Accumulation of lipoprotein X is noted in cholestatic liver disease. Its potential as an atherogenic particle is as yet unclear.

**lithiasis** The formation of stones of any kind (e.g., gallstones).

**lithogenesis** The formation of stones in the gallbladder or kidneys.

**lithotomy** Body position in which the patient lies on his/her back on the examining table, with hips and knees fully flexed; also called dorsosacral position. For obstetric procedures, the buttocks are at the edge of the table and the feet are held in stirrups.

**liver biopsy** A procedure in which a needle is placed into the liver and a small portion of the liver is removed for histological examination; most commonly done through the skin as an outpatient procedure.

**liver-bowel transplant** The combined simultaneous transplantation of a liver and jejuno-ileum, requiring removal of the native liver.

**liver segment** Any portion of the liver defined by an independent blood supply.

**lobectomy** The excision of a lobe of an organ, e.g., liver.

**longevity** The length of time an individual survives; for humans, 120 years is considered the maximal life span.

**looping** A suboptimal curvature of the colonoscope within the colon, making it difficult to advance the colonoscope.

**low-density lipoprotein (LDL)** The major carrier of cholesterol in plasma of humans. LDL is formed predominantly from very-low-density lipoprotein as a result of catabolism of the core triglyceride, analagous to the formation of chylomicron remnants.

**lower esophageal sphincter** A ring of circular muscle that closes the orifice between the esophagus and the stomach.

**lower gastrointestinal** Pertaining to the colon.

**Lp(a)** Lipoprotein A, a modified form of LDL in which a large glycoprotein [apo(a)] is covalently bound to the apoB. Serum levels of Lp(a) are genetically defined. Its association with atherosclerosis is not completely established.

**lumen** A cavity within a tubular organ, as in the gastrointestinal tract.

**lumenal surveillance peptides** Molecules that are constantly present within the gut lumen; their predominant role is to stimulate repair at sites of injury, acting in a "surveillance" fashion.

**lymph** Fluid that is collected from the tissues throughout the body and transported via the lymphatic vessels to the venous blood.

**lymphangioma** A well-circumscribed nodule of lymphatic vessels; the vessels vary in size, are usually greatly dilated, and are lined with normal endothelial cells. They are most frequently found in the neck, axilla, arm, mesentery, and retroperitoneum.

**lymphatics** Vessels that contain or convey lymph; lymphatics of the small intestine are the site where absorbed fat is drained.

**lymphocytic colitis** A condition of chronic colitis, characterized by watery diarrhea, no gross radiographic or endoscopic abnormality, and biopsies showing prominent increase of lymphocytes within the surface and upper crypt epithelium.

**lymphoid follicular hyperplasia** Increased growth and abundance of lymphoid follicles, often seen in pathologic specimens of patients with diversion proctitis and colitis.

## M

**magnetic resonance cholangiopancreatography** Visualization of the bile ducts and pancreatic duct, achieved during magnetic resonance imaging; does not require contrast medium to be injected into the ducts. The ducts are visible because of differences between the magnetic properties of the biliary/kpancreatic fluid and surrounding tissues.

**magnetic resonance imaging (MRI)** A technique that is based on the interaction between an external magnetic field and a nucleus that possesses spin. The patient is exposed to energy at a specific, correct frequency; this energy is absorbed and a short time later is released, at which time it can be detected and processed to yield images.

**major histocompatibility complex (MHC)** The genetic region on the short arm of chromosome 6 encoding groups of highly polymorphic surface proteins that are expressed on the surface of all living cells and that are important in antigen presentation and shaping of the immune repertoire.

**malabsorption** Impaired or incomplete absorption of dietary nutrients by the intestine; can result from any abnormality in the process of digestion and/or absorption of nutrients.

**maladaptive coping** Beliefs and strategies on how to master a crisis or a problem that are not helpful or even counterproductive, e.g., catastrophizing, internalization.

**maldigestion** Disorder of the process whereby ingested food is converted into material suitable for assimilation by the gastrointestinal mucosa.

**Mallory-Weiss tear** A traumatic tear of the lining of the lower esophagus or upper stomach, often caused by vomiting.

**manometric recording** A graphic measure of changes in pressure in localized regions of the digestive tract, indicating contractile behavior of the musculature.

**manometry** Examination measuring pressure in the gastrointestinal tract.

**marasmus** Generalized starvation with loss of body fat and protein.

**Marfan syndrome** A heritable disorder of the connective tissue (caused by a mutation in the fibrillin gene) that affects many organ systems.

**marginal ulcers** Peptic ulcers that occur at or near a surgically created gastroduodenostomy or gastrojejunostomy.

**mass movement** Ultrarapid propulsion of a large bolus of digesta over a sizable length of the small bowel or colon.

**mast cell** A cell of hematopoietic origin that matures within tissues and functions in both innate and acquired immunity through the release of mediators of inflammation following specific activation.

**mastication** The act or process of chewing food.

**mastocytosis** A collective term for a group of rare disorders characterized by an abnormal accumulation of mast cells in one or more organ systems.

**mature hepatocyte** A parenchymal epithelial liver cell expressing liver genes expected in fully differentiated cells.

**McBurney's point** The point in the right lower quadrant of maximal tenderness (overlying the appendix), described by Charles McBurney as being between 1.5 and 2 inches from the anterior iliac spine along the oblique line to the umbilicus.

**M cell** A specialized type of epithelial microfold cell that is found in the epithelium overlying organized lymphoid follicles (Peyer's patches). Endocytosis and transport of intestinal microbial organisms and large molecules from the lumen into the underlying lymphoid tissues are the main functions of M cells.

**mechanoreceptors** Molecules on sensory neurons that detect and signal mechanical energy changes such as contractile tension or stretch of a muscle.

**Meckel's diverticulum** A 2-cm to 6-cm outpocketing of the ileum along the antimesenteric border, usually located 50 to 180 cm proximal to the ileocecal valve.

**meconium** A dark greenish mass of desquamated cells, mucus, and bile that accumulates in the fetal bowel and is typically discharged shortly after birth.

**medullary thyroid carcinoma** A malignant tumor of the thyroid gland; the most common tumor found in multiple endocrine neoplasia types 2a and 2b.

**megacolon** A condition in which the colon has abnormally large dimensions.

**megaloblastic anemia** Anemia characterized by peripheral macrocytosis and bone marrow containing megaloblasts due to impaired DNA synthesis. Cobalamin deficiency along with folate deficiency leads to this condition.

**Meig's syndrome** A triad of benign ovarian fibroma with ascites and right-sided pleural effusion.

**Meissner's plexus** The network of neurons located within the submucosa of the gastrointestinal tract; primarily involved with the transmission of sensory information between the central nervous system and the peripheral end organ.

**melena** The passage of dark black stool, representing blood typically from an upper gastrointestinal source.

**MEN** A syndrome associated with multiple endocrine neoplasms; three types are recognized (1, 2a, and 2b)

and types 1 and 2a are associated with hyperparathyroidism.

**Menetrier's disease** A form of gastropathy characterized by hyperplasia of the lining epithelium and hypertrophy of the mucosa, with or without inflammation (gastritis).

**meningocele (meningomelocele)** Failure of closure of the spinal cord in the lower back that results in a protrusion of skin containing spinal tissue.

**mesenteroaxial gastric volvulus** A condition in which the stomach folds upon itself along its short axis.

**mesentery** A double layer of peritoneum attached to the abdominal wall, enclosing in its fold certain organs of the abdominal viscera.

**mesocaval shunt** A surgically created shunt promoting flow from the superior mesenteric vein into the inferior vena cava, bypassing an occluded hepatic outflow tract.

**mesoderm** One of the three germ layers formed by the process of gastrulation. Mesodermal cells give rise to mesenchymal tissue and the muscle layers of the gastrointestinal tract.

**mesothelium** A layer of cells lining an internal cavity of the body, such as the peritoneal or pericardial cavities.

**meta-analysis** The analysis of combined data from multiple epidemiological studies, for the purpose of integrating the findings; often used to increase statistical power and/or provide a broader perspective.

**metabolic pancreatitis** A pancreatic disorder related to abnormalities such as hyperlipidemia or hypercalcemia; can cause acute or recurrent pancreatitis but is extremely rare in pediatrics.

**metacercaria** An encysted trematode stage; the life cycle continues following consumption by a definitive host.

**metachromasia** The result obtained when a stain is applied to cells or tissues and gives a color different from that of the stain solution.

**metachronous neoplasia** Tumors (adenomas, adenocarcinomas, or a combination of both) that are diagnosed at different points in time; in clinical practice, metachronous neoplasms may refer to newly formed and newly discovered tumors.

**metaplasia** Reversible change in which one adult cell type is replaced by another adult cell type that is not normally present in that area; may represent an adaptive substitution of cells in response to environmentally mediated injury. The finding of metaplasia can serve as a marker that the patient has a chronic inflammatory lesion; if persistent, cancer transformation may occur.

**methotrexate (MTX)** A dihydrofolate reductase inhibitor. MTX and its metabolites inhibit the enzymes responsible for folate metabolism that result in anti-proliferative and cytotoxic effects on hematopoietic cells. Has been used with some efficacy in Crohn's disease.

**methylation** The process of adding a methyl group onto an existing molecule of a base pair that changes (often impedes) the ability of nuclear enzymes to "read" the genetic code.

**methylmalonic acid (MMA)** A metabolite of methylmalonyl-coenzyme A1 that is excreted in the urine. Cobalamin deficiency leads to the accumulation of MMA; measurement of MMA in plasma is utilized for the diagnosis of cobalamin deficiency.

**micelles** Structures formed by association of bile salts and containing fat digestion products; found in the lumen of the small intestine.

**microhamartoma** A rare, benign lesion of hepatocytes and biliary epithelium encased by a fibrous stroma.

**microlithiasis** Microscopic precipitates in bile that can be visualized with ultrasonography or bile microscopy.

**microsatellite** A short, repetitive DNA sequence; repeats consist most commonly of mononucleotide repeats, dinucleotide repeats, trinucleotide repeats, or occasionally tetranucleotide or pentanucleotide repeats. Poly(A) or dinucleotide repeats are the most common of these. These repetitive sequences are highly prone to insertion or deletion mutations during DNA replication, and require DNA mismatch repair activity for faithful replication.

**microsatellite instability** Mutational signature in which ubiquitous errors are seen in repetitive DNA sequences as a consequence of losing mismatch repair activity.

**microscopic colitis** A syndrome of watery diarrhea with colonic mucosal abnormalities that include the histologic features of either collagenous colitis or lymphocytic colitis.

**microsomal triglyceride transfer protein (MTTP)** A resident endoplasmic reticulum protein that is absolutely required for the transfer of complex lipid to the growing polypeptide chain of apolipoprotein B. Defects in the gene encoding MTTP result in the autosomal recessive disorder abetalipoproteinemia.

**microsomes** Small particles in the cytoplasm of a cell, typically consisting of fragmented endoplasmic reticulum to which ribosomes are attached.

**microvilli** Fingerlike extensions along the apical surface of intestinal mucosal cells. On enterocytes, microvilli increase the absorptive surface of the cell; on endocrine cells, microvilli allow potential stimuli greater exposure to their targets (e.g., receptors).

**mid-arm muscle circumference (MAMC)** An index of body mass derived by measuring the triceps skinfold (TSF) and mid-upper arm circumference (AC) midway between the shoulders and the elbow.

**migrating motor complex** A specific pattern of small intestinal motility that begins when digestion of a meal is complete and ends with the intake of the next meal. Characterized by three successive patterns of contractions (Phases I, II, and III) that are cyclically recurring as long as fasting is maintained and that disappear after eating. Also called interdigestive motility complex.

**milk intolerance** Clinical symptoms induced by the ingestion of milk; can be due to either lactose intolerance or milk protein allergy.

**mini-perforation** A small rent in the bowel, which typically is contained by the overlying omentum and heals without the need for surgical repair.

**miracidium** A ciliated larval trematode stage that is released from the egg.

**Mirizzi syndrome** Obstruction of the common hepatic duct due to extrinsic pressure by a stone in the cystic duct or the gallbladder neck.

**mismatch repair gene** A gene responsible for repairing small DNA errors or mismatches that occur during DNA replication.

**missense mutation** A mutation that changes a codon for a specific amino acid to a different amino acid and results in a change in the amino acid sequence of a protein.

**mitochondrion** (*pl.* **mitochondria**) A spherical or elongated organelle in the cytoplasm of the cell, containing genetic material and many enzymes important for cell metabolism, including those responsible for the conversion of food to usable energy.

**mitogen-activated protein (MAP) kinases** Enzymes involved in the transmission of signals from cytokine and other receptors to downstream transcription factors.

**mixed diaphragmatic hernia** A combination of sliding and paraesophageal hernia.

**mixed dysrhythmias** Gastric dysrhythmias characterized by intermittent bradygastria and tachygastria.

**mixed hepatitis** A combination of cytolytic and cholestatic hepatitis.

**mixing movements** The specific pattern of small intestinal motility that starts with the ingestion of a meal and accomplishes mixing of the contents in the lumen.

**molecular chaperones** Intracellular helper proteins that assist in the proper folding of polypeptides into their functional structures.

**monogenean** Of a parasite, having a single host.

**monosynaptic spinal reflex** A neural reflex circuit in the spinal cord consisting of a sensory neuron and a motor neuron with a single synaptic connection between the two.

**monoxenous** Of a parasite, requiring only one host to complete the entire life cycle.

**morbid obesity** A severe form of obesity that is frequently associated with a variety of conditions such as diabetes, heart disease, and hypertension. Any person with a body mass index equal to or greater than 40kg/m$^2$ is considered morbidly obese.

**Morgagni hernia** A diaphragmatic defect in the anterior chest at the sternocostal junctions.

**motilin** A hormone released by enteroendocrine cells in the gut.

**motility** See GASTROINTESTINAL MOTILITY

**motor neurons** Neurons with cell bodies located in the myenteric plexus and axons projecting to longitudinal and circular muscle layers.

**mucin** A protein that has many carbohydrate molecules covering its surface; the dominant protein of mucous.

**mucosa** The most highly differentiated layer of the gastrointestinal tract, comprising the epithelium, basement membrane, lamina propria, and layer of smooth muscle known as muscularis mucosae. Tissue specialization and surface shape are correlated with functional differentiation along the tract.

**mucosa-associated lymphoid tissue (MALT)** An organized immune system found in mucosal sites. Gut-associated lymphoid tissue is a component of MALT; these are inductive sites where luminal antigens are processed.

**mucosa-associated lymphoid tissue (MALT) lymphoma** A low-grade primary B-cell gastric lymphoma associated with *Helicobacter pylori* infection; a MALT-like organization of the stomach is induced by chronic gastric inflammation and development of lymphoma.

**mucosal** Pertaining to the mucosal layer.

**mucosal eosinophilic gastroenteritis** An eosinophilic infiltration primarily in the mucosal layer, resulting in vomiting, diarrhea, and abdominal pain.

**mucosal homeostasis** A complex array of protective mechanisms coordinated by neural and other control systems to ensure that the mucosa survives undamaged the onslaughts that occur during digestion; the gastrointestinal mucosa is endangered by toxic, antigenic, and pathogenic food ingredients as well as by potentially harmful secretory products such as pepsin and acid.

**mucosal integrity peptides** Molecules that are constitutively expressed in the mucosa and which function to maintain normal mucosal integrity.

**mucosal restitution** An early phase of gastrointestinal mucosal repair whereby damaged cells slough off and are replaced by viable cells.

**mucous (mucus) cells** Salivary gland cells that synthesize, store, and secrete large amounts of mucins.

**multiacinar necrosis** A histological pattern of severe liver inflammation in which the inflammatory infiltrate and evidence of hepatocyte damage extend across and collapse lobules of liver tissue.

**multidetector computed tomography (CT)** An advancement in helical CT in which multiple detectors, rather than a single detector, are employed to acquire the data. This technology allows for flexibility in slice thickness and faster scanning ability. Thinner slices increase diagnostic ability and may be used as the source data for a broad range of three-dimensional applications.

**multiorgan failure** Malfunction progressing to complete failure of vital organs, occurring after shock and infection in a trauma patient.

**multiple endocrine neoplasia type 1 (MEN-1)** An autosomal dominantly inherited disorder associated with endocrine tumors of the parathyroid, pituitary, and endocrine pancreas, as well as in some patients with tumors of other endocrine glands and skin manifestations.

**multivisceral transplant** Transplantation of the stomach, pancreas, and small intestine, and sometimes other organs, which may include the liver and/or kidney.

**Münchausen by proxy syndrome** Illness intentionally produced in a child by a parent who wants to be seen as concerned and caring.

**Münchausen syndrome** Self-inflicted or feigned illness in an individual as a conscious attempt to gain attention and sympathy.

**mural stratification** Computed tomography visualization of all three layers of the gut: mucosa, submucosa, and muscularis propria. Most benign causes of gastrointestinal pathology result in mural thickening of the gut with preservation of mural stratification. Malignant disorders generally cause wall thickening with loss of mural stratification.

**muscarinic receptors** Receptors for acetylcholine present in salivary gland cells that act to increase intracellular $Ca^{2+}$.

**muscular eosinophilic gastroenteritis** Eosinophilic infiltration extending into the muscular layer of the gastrointestinal tissues, resulting in obstructive symptoms and stricture formation.

**muscularis externa** Smooth muscle layer surrounding the mucosa and submucosa. It is composed of an inner circular and outer longitudinal layer, which function in coordination to propel and mix luminal contents.

**mutagenic** Of or pertaining to any chemical or physical environmental agent capable of inducing genetic mutations or increasing the mutation rate.

**mutation** A permanent transmissible change in the genetic material, usually in a single gene.

***Mycobacterium avium* complex** A member of the *Mycobacterium* family that causes diffuse systemic infection in immunocompromised patients; can lead to cachexia, fever, and weight loss.

***Mycobacterium tuberculosis*** An acid-fast intracellular bacterium that causes tuberculosis. The primary site of infection is the lung but infection can involve the gastrointestinal tract and can spread throughout the body, where it is termed miliary tuberculosis.

**myenteric plexus (Auerbach's plexus)** A system of nerves and ganglia lying within the longitudinal and circular muscle layers of the intestine. The nerves of the system innervate numerous targets, including the myenteric externa, mucosa, and sympathetic prevertebral ganglia.

**myocardial infarction** Blockade of blood flow in one or more major vessels of the heart.

**myocardial ischemia** Reduced blood flow to the heart.

**myoclonus** Rapid involuntary alternate muscular contractions and relaxations resulting from paroxysmal outflow from the central nervous system to the involved muscles.

**myoepithelial cells** Contractile cells with branching processes surrounding end-pieces; their contractions force saliva from the end-pieces into the ducts.

**myogenic** Originating in the musculature of an organ.

**myopathic** Pertaining to diseases of the musculature.

**myxedema** Thyroid deficiency in adults associated with skin and soft tissue edema; generally used to connote a more severe (advanced) case of hypothyroidism with accumulation of mucopolysaccharide material in soft tissues, body cavities, and organs.

## N

**nasogastric tube** A long, thin tube that is inserted through the nose, down the throat, and into the stomach for the purpose of introducing liquid nourishment (tube feeding).

**necrosis** Death of cells or tissues through injury or disease.

**necrotizing enterocolitis** Extensive ulceration and necrosis of the ileum and colon in premature infants in the neonatal period; possibly due to perinatal intestinal ischemia and bacterial invasion.

**needle biopsy** A surgical procedure to obtain tissue from deep within the body, e.g. liver tissue, by inserting a specialized needle through the skin.

**negative appendectomy** Removal of a grossly and histologically normal appendix when appendicitis is expected.

**nematode** A nonsegmented roundworm of the phylum Nematoda; may be free-living or parasitic.

**neoadjuvant** Before surgery; preoperative.

**neoadjuvant therapy** A cancer treatment strategy of preoperative administration of chemoradiation aimed at increasing the number of patients able to complete multimodality therapy.

**neoangiogenesis** Growth of new blood vessels in tissues.

**neoplasia** The pathological process that results in the formation and growth of a tumor.

**neoplasm** Abnormal tissue growth that is uncontrolled and progressive but can be either benign or malignant.

**neoplastic** Describing rapidly growing cells that are not necessarily transformed.

**nestin** An intermediate filament protein characteristic of undifferentiated cells during cortical and enteric nervous system development.

**neural crest** An ectodermal embryonic structure that arises from the neural primordium lateral borders when they form the neural tube.

**neural crest cells** Cells originating from the neural crest, a subpopulation of which migrate into the wall of the developing intestine and are the source of virtually all neurons and glial cells of the peripheral nervous system.

**neural tube defect** A congenital defect of the neural tissue affecting the spinal cord, spine, brain, and skull, resulting in miscarriage, fetal or neonatal death, or disability.

**neurocrine action** Activity elicited from a neuron in response to factors released by an adjacent cell or neurone.

**neurodegenerative disease** Any slowly progressive disease in the central or peripheral nervous system resulting from neuronal damage and/or neuronal death.

**neuroendocrine system** An array of cells with both neural and endocrine characteristics; thought to arise from cells that migrate from the dorsal neural crest area of the embryo during embryological development.

**neuroendocrine tumors** Growths that may occur in many tissues throughout the body; produce a variety of

peptides and other agents, some of which are biologically active and produce distinctive hormonal syndromes. These include carcinoid tumors, pheochromocytomas, pancreatic islet cell tumors, and medullary carcinoma of the thyroid.

**neuroleptics** Drugs used to treat various psychiatric disorders including schizophrenia.

**neurolysis** Destruction of nerves to produce pain relief

**neuromedin B** A 10-amino-acid mammalian peptide isolated from porcine spinal cord that resembles the frog peptides, ranatensin and litorin.

**neuromodulator** A substance that can alter the release or effect of a neurotransmitter.

**neuropathic** Pertaining to disordered function caused by disease or malfunction of the nervous system.

**neuropeptide** A short chain of amino acids that is expressed by specific neurons and serves as an extracellular messenger of those neurons.

**neurotransmitter** A chemical released by neurons in the brain or peripheral nervous system to communicate with other neurons.

**neutropenic** Deficient in neutrophils.

**nitric oxide (NO)** A gas produced by cells of the brain, blood vessels, and the immune system; it mediates smooth muscle relaxation through activation of guanylate cyclase and production of cyclic GMP.

**nitric oxide synthase-2** A protein that produces abundant bactericidal nitric oxide in response to inflammation.

**nitric oxide synthase-3** A protein that continuously produces small amounts of nitric oxide to maintain normal blood pressure.

**nitrogen balance** The net difference between intake of nitrogenous sources of nutrients and nitrogen losses, principally in the urine. Nitrogen intake is estimated by protein intake in grams divided by 6.25. The 24h urinary urea nitrogen excretion in grams plus 4 is used to estimate nitrogen output.

**nociceptive** Describing an unpleasant or painful sensation.

**nociceptor** A receptor on a sensory nerve that signals pain to the central nervous system.

**nocturia** Excessive urination at night.

**NOD2** A gene within the IBD1 locus that has been associated with Crohn's disease. It codes for a protein involved in the innate immune response to bacterial products.

**nodose ganglia** Sensory ganglia containing the cell bodies of afferent neurons that innervate the thoracic and abdominal viscera. These neurons project centrally to make synaptic connections in the nucleus of the tractus solitarius and peripherally to terminate in the viscera.

**non-beta islet cell tumors** Pancreatic endocrine tumors arising from cells other than the insulin-producing beta cells of the islets of Langerhans.

**noncaseating granuloma** An aggregation of epitheloid macrophages, lymphocytes, and multinucleated giant cells.

**noncontrast computed tomography (CT) scans** Images obtained on CT without intravascular or intralumenal contrast material. This is a good technique for evaluating kidney and ureter stones but limits the sensitivity in detecting gastrointestinal pathology.

**nonketotic hyperosmolar state** A syndrome associated with little or no ketoacid accumulation in blood, hyperglycemia, increased plasma osmolality, and neurological abnormality.

**nonnucleoside reverse transcriptase inhibitor** A class of drugs used in combination as highly active antiretroviral therapy to treat HIV disease. Examples include efavirenz and nevirapine.

**nonsteroidal antiinflammatory drugs (NSAIDs)** Chemical compounds that are effective in reducing inflammation and treating pain and fever; can cause injury to the gastrointestinal tract as their principal side effect. Unlike glucocorticoids, NSAIDs do not impact endocrine and immunological functions and are therefore favored as therapeutic agents for long-term treatment of chronic inflammatory conditions such as rheumatoid arthritis. Widely used NSAIDs include oxicam, salicylate (aspirin), acetic acid (indomethacin, diclofenac), fenamate, propionic acid (ibuprofen, naproxen), and pyrazole.

**nontyphoidal *Salmonella* (NTS)** The most important agents of foodborne illness, second only to campylobacteriosis in incidence. More than 2400 serotypes of NTS have been identified; all are now considered members of a single species, *Salmonella enterica*.

**non-ulcer dyspepsia** A syndrome of recurrent chronic epigastric pain with no ulceration found on gastroscopy.

**norovirus** The recently adopted name to designate the genus of the viral family *Caliciviridae*; the viruses in this genus were previously called Norwalk-like viruses or small round structured viruses.

**nosocomial** Hospital-acquired; as a result of a stay in or visit to a hospital.

**NSAIDs** See NONSTEROIDAL ANTI-INFLAMMATORY DRUGS.

**nuclear factor kappa B (NF-kB)** A conserved signal transduction pathway critical for the activation of innate immune and inflammatory responses.

**nucleation** A term for the initial precipitation of solid cholesterol crystals from supersaturated bile. An initial step in gallstone formation.

**nucleus ambiguous** The origin of motor neurons supplying the striated pharyngeal and esophageal muscles.

**nucleus of the tractus solitarius** Brainstem nucleus receiving vagal sensory input; the neurons project to the dorsal motor vagal nucleus to complete the brainstem circuit for vago-vagal reflexes and disseminate sensory information to higher brain regions.

**nutcracker esophagus** Vigorous peristaltic contractions of the esophageal body; frequently associated with chest pain or other symptoms, such as depression, anxiety, and somatization, without a clear underlying cause and with uncertain clinical significance.

**nutritional pancreatitis** A form of nonalcoholic chronic pancreatitis prevalent in India and other tropical countries.

## O

**obesity** An increase in body weight significantly beyond the limits of skeletal and physical requirements, as the result of an abnormal increase in the proportion of fat cells, mainly in the viscera and subcutaneous tissues. May be exogenous (caloric intake greater than metabolic needs) or endogenous (dysfunction of the endocrine or metabolic systems). Can be defined as a body mass index $>30 kg/m^2$.

**octreotide** A synthetic peptide that is related to the naturally occurring peptide somatostatin; it has therapeutic uses and can be radiolabeled for use as a diagnostic agent.

**odynophagia** Pain experienced when swallowing food or liquid.

**olfactory** Relating to the sense of smell.

**oligoarthritis** A form of arthritis that involves more than one joint but a relatively small number of joints.

**oligohydramnios** A condition of insufficient amniotic fluid.

**oligopeptide** An oligomer of amino acid units joined by peptide linkages. The term is commonly used to refer to structures containing 4 to 25 amino acid residues.

**oligosaccharide** A carbohydrate compound in which monosaccharide units are joined by glycosidic linkages. The term is commonly used to refer to defined structures having three to nine monosaccharide units.

**omeprazole** The prototypical, clinically used proton pump inhibitor.

**oncogene** A genetic sequence encoding a product that promotes cell transformation or cancer formation. Oncogenes usually result from gain-of-function mutations of normal genes, called proto-oncogenes.

**onco-neural antigens** Antigens shared by tumor cells and neural tissues that are likely capable of triggering the immune response involved in the neuropathophysiology of paraneoplastic syndrome.

**ontogenic regulation** A process controlling developmental changes, as in a transport event.

**oocyst** The cystic stage of the Apicomplexa, resulting from sporogony (e.g., *Plasmodium*, *Cryptosporidium*, *Toxoplasma*, *Cyclospora*).

**operculum** The hinged portion of a trematode egg through which the larva hatches.

**ophthalmoparesis** A weakness of the eye muscles.

**optokinetic drum** A device with alternating black and white vertical stripes that is rotated around a subject to provoke motion sickness.

**oral contraceptive** An oral agent containing estrogen or estrogen and progesterone and used in the prevention of pregnancy.

**orexigenic** Stimulating the appetite.

**organelles** Small intracellular "organs" that perform specialized tasks.

**organic anion transport protein** A polypeptide in rat liver; a glycoprotein with 670 amino acids. The human analogue also consists of 670 amino acids and shows a 67% amino acid homology to the rat liver protein.

**organoaxial gastric volvulus** A condition in which the stomach twists along its long axis.

**organoleptic measurement and score** A method of scoring odor intensity by smelling the patient's breath. Observation conditions must ensure that breath air is not diluted with room air.

**Osler node** A tender, raised, cutaneous lesion, typically on the finger pads; characteristic of infective endocarditis.

**osmolyte** A molecule that can be dissolved in a solvent (most commonly water) and thereby contribute to the total concentration of particles in the solvent, adding to the osmolarity.

**osmotic diarrhea** High-output diarrhea resulting from ingested, unabsorbed nutrients, which act as osmotic agents, drawing free water into the intestinal lumen.

**osteoma** A benign, slow-growing tumor composed of well-differentiated, densely sclerotic, compact bone, usually arising in the membrane bones, particularly the skull and fascial bones.

**osteomalacia** Defective mineralization of the organic matrix, resulting in excessive accumulation of osteoid in the bone tissue and increased propensity of the bones to bow or fracture under the weight of the body.

**osteopenia** A condition of decreased bone mass, defined by the World Health Organization as a bone mineral density between 1.0 and 2.5 standard deviations relative to the ideal peak bone mass.

**osteoporosis** A skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fractures, defined by the World Health Organization as a bone mineral level lower than 2.5 standard deviations from the ideal peak bone mass.

**ostomate** An individual undergoing an ostomy, usually an ileostomy or colostomy.

**ostomy** An operation to create an artificial opening through which body wastes may exit.

**ostopenia** Reduced bone formation.

**outer inflammatory protein A** An outer inflammatory protein of *Helicobacter pylori* that is involved in mucosal inflammation. The protein is considered a virulence factor of the bacterium and its presence is associated with increased mucosal inflammation.

**outlet dysfunction** A constellation of disorders in which normal defecation is disturbed by organic or functional abnormalities of the anorectum.

**overexpression** The production of excessive amounts of a product by cells because extra copies of the gene encoding the product have been introduced into the cell chromosomes.

**overweight** Higher than normal body weight for one's height, body build, and age; can be defined as a body mass index in the range of $25-29.9 kg/m^2$.

**oxidative metabolizing enzymes** Enzymes that render drugs and other xenobiotics both less biologically active and more water soluble for renal or biliary excretion. The principal enzymes involved in this process are the

microsomal mixed-function oxidases of the cytochrome P450 system.

**oxidative stress** Increased generation of reactive oxygen species or free radicals, including superoxide anions, hydrogen peroxide, and hydroxyl radicals; occurs as a consequence of accumulation of fat within hepatocytes. The reactive oxygen species or free radicals seem to induce chemotaxis and accumulation of inflammatory cells in the liver.

## P

**P450 induction** Increased synthesis of P450 enzymes following extended exposure to certain drugs or substances, resulting in accelerated metabolism of other drugs.

**P450 inhibition** Specific inhibition of cytochrome P450 enzymes by certain drugs or foods; delays the metabolism and augments the pharmacologic effects of other drugs that are substrates of the same enzyme.

**pagophagia** The act or habit of eating ice.

**palliation** Treatment designed to relieve a patient's symptoms without the intent to cure the disease causing the symptoms.

**palliative** Relieving symptoms without curative intent.

**palpable purpura** Visible and often palpable discrete cutaneous hemorrhage, typically in dependent areas. It is occasionally confluent and extensive.

**pancreatic cystic neoplasms** Pancreatic tumors that arise from parenchymal cells and often form cystic shapes seen in imaging studies.

**pancreatic duct (duct of Wirsung)** The primary secretory channel of the pancreas.

**pancreatic duodenal homeobox factor-1** A patterning transcription factor required for the differentiation of the pancreas.

**pancreatic insufficiency** Decreased secretion of digestive enzymes or insulin to the extent that malabsorption or diabetes mellitus appears. Malabsorption typically manifests with steatorrhea, the presence of more than 7% of dietary fat in the stool.

**pancreatic intraepithelial neoplasia** Areas of focal ductal proliferation adjacent to infiltrating pancreatic cancers that may be precursor lesions to pancreatic adenocarcinoma.

**pancreatic islet-acinar portal system** An arterial supply network that connects the pancreatic islet cells with the exocrine cells.

**pancreatic islet cells** Small groups of cells found throughout the pancreas; subdivided into alpha, beta, and delta islet cell types, which produce glucagon, insulin, and somatostatin, respectively.

**pancreaticoduodenectomy** Surgical excision of the head and uncinate process of the pancreas by en bloc resection of the distal stomach and duodenum to the ligament of Treitz, common bile duct, and head of the pancreas. Also known as a Whipple procedure.

**pancreatic pseudocyst** A non-epithelial-lined collection of pancreatic secretions.

**pancreatic rest** Ectopic pancreatic tissue located in the wall of the stomach or small intestine.

**pancreatic stellate cells** Cells located between acini that contain vitamin A; cells of stellate morphology that respond to cytokines with the production of collagen, leading to fibrosis.

**pancreatic triglyceride lipase** A specific enzyme produced and secreted by pancreatic acinar cells; primarily responsible for intestinal digestion of triglycerides.

**pancreatitis** Inflammation of the pancreas.

**Paneth cells** Cells normally found only at the base of the crypt of Lieberkuhn in the small intestine; responsible for secreting lysozyme and antimicrobial factors.

**papillary stenosis** Narrowing or stricture of the papilla of Vater, the common exit site of fluid passing through the common bile and pancreatic ducts.

**paracellular transport** Vectorial transport of material through the extracellular spaces between adjacent epithelial cells; results in net movement of material between the two compartments faced by epithelial cells.

**paracrine** Describing the secretion of a hormone from a cell, with the hormonal effect exerted on an adjacent cell.

**paraesophageal hernia** A defect in which part or all of the stomach protrudes through the esophageal hiatus alongside the esophagus.

**paralytic ileus/adynamic ileus** A condition in which the prolonged absence of intestinal motility is pathologic.

**paraneoplastic syndrome** An autoimmune pathology in tissues of patients with certain forms of cancer.

**pararenal aortic aneurysm** A classification for a juxtarenal aneurysm (near, but not involving, the renal artery orifices) or a suprarenal aneurysm (involving the renal arteries but not the superior mesenteric artery).

**parasite** An organism that is physiologically dependent on another organism and extracts its nutrients from this host. More specifically, when the term is used for organisms colonizing humans, it frequently refers to protozoans and helminths and sometimes ectoparasites (e.g., ticks, lice).

**paravertebral ganglia** Ganglia located alongside and parallel to either side of the vertebral column.

**parenchymal extinction** Process of focal loss of hepatocytes, usually by a mechanism of ischemia. An extinction lesion is the histologic product of this process.

**parenteral** By means other than the gastrointestinal tract, such as via intravenous injection.

**parenteral nutrition (PN)** The infusion of all essential nutrients by the intravenous route, bypassing the gastrointestinal tract.

**parenteral transmission** Acquisition of an infection by exchange of the infectious agent via blood or blood-contaminated body fluids.

**parietal cell** One of the cell types of the gastric epithelium; responsible for acid production and secretion into the gastric lumen.

**parotid glands** The major serous salivary glands located bilaterally under the ear.

**Pathergy** Excessive inflammatory reaction to tissue trauma. Characteristic of Behçet's disease, but also seen in pyoderma gangrenosum.

**pathogenicity island** A mobile genetic element, often encoding virulence genes; found in many pathogenic bacteria and propagated by horizontal gene transfer.

**pathognomonic** Characteristic or indicative of a disease; denoting especially one or more typical symptoms, findings, or pattern of abnormalities specific for a given disease and not found in any other condition.

**P-ATPases** A family of adenosine triphosphate-dependent metal transporters that have specificity for divalent cations.

**PDX-1** Pancreas duodenum homeobox 1, the patterning transcription factor required for early development of the embryonic pancreas.

**peliosis hepatis** A condition associated with blood-filled cavities in the liver; a disease is found mostly in patients with acquired immune deficiency syndrome and anabolic steroid users.

**pelvic floor dyssynergia** Inappropriate contraction or failure to relax the pelvic floor and/or anal sphincter muscles during attempts to defecate, resulting in the impedance of stool passage.

**penetrance** The frequency of expression of a genotype; a trait has reduced penetrance if it is expressed less than 100%.

**pepsigogue** An agent that stimulates pepsinogen secretion.

**pepsin** A protein secreted in the stomach that begins cleaving ingested proteins into smaller polypeptides. It functions optimally in the acid environment of the stomach, at pH 1–3, and is inactivated when the acid is neutralized, at pH 5 or higher, in the duodenum.

**pepsinogen** Protein precursor of pepsin synthesized and secreted by gastric chief cells.

**peptic ulcer** A loss of tissue extending through the mucosa into the submucosa, in the esophagus, stomach, or duodenum, due to acidic gastric secretions.

**peptic ulcer disease** A disorder of the upper gastrointestinal tract (esophagus, stomach, and duodenum), characterized by inflammation and ulceration.

**peptide** A short chain of amino acids.

**peptide bond** The covalent chemical bond between two amino acid residues.

**peptide YY** A distal gut peptide that is released in response to fat and is involved in the ileal brake and jejunal brake responses.

**percutaneous endoscopic gastrostomy (PEG)** An endoscopic procedure during which a feeding tube is placed between the stomach and the anterior abdominal wall to allow for direct feeding into the stomach. The most common indications for PEG tube placement are neurologic conditions associated with impaired swallowing and neoplasms of the oropharynx, larynx, and esophagus.

**percutaneous ethanol injection** Ablative therapy in which a needle is inserted into the mass and ethanol is injected, with the goal of killing all the tumor cells.

**percutaneous transhepatic cholangiography** A procedure that permits direct visualization of the biliary tree via percutaneous placement of a fine needle through the lower right chest wall through the hepatic parenchyma and into the right or left bile duct. Injection of radiopaque contrast media enables the visualization of the proximal biliary tree and common bile duct.

**perforation** An abnormal opening in a hollow organ or viscus.

**periductal fibrosis** Fibrosis occurring around the bile ducts.

**perineal protectomy** A surgical procedure, performed via the anus, that excises redundant rectum and reconnects the two remaining ends.

**perineum** The external region between the anus and the genitalia.

**perinuclear anti-neutrophil cytoplasmic antibody** A distinct form of anti-neutrophil cytoplasmic antibody seen in inflammatory bowel disease. It is characterized by a perinuclear staining pattern and is present in up to 65% of ulcerative colitis patients.

**periodic acid-Schiff stain** A histochemical stain that highlights glycogen and glycoproteins.

**peristaltic reflex** The basic local motor reflex that is responsible for caudal propulsion of intraluminal contents.

**peritoneal lavage** A technique to access hemorrhage into the abdominal cavity whereby a small tube is inserted into the space and fluid is instilled into the cavity and then removed to determine whether free blood is present.

**peritoneal mesothelioma** A rare malignant tumor arising from the peritoneal lining of the abdominal cavity.

**peritoneum** The serous lining of the abdominal cavity; the parietal peritoneum lines the abdominal wall and the visceral peritoneum covers the organs.

**peritonitis** Inflammation of the peritoneal linings of the abdominal cavity; may be of infectious, chemical, or unknown origin.

**pernicious anemia** An anemic condition characterized by larger than normal (megaloblastic) red blood cells. Insufficient gastric production of intrinsic factor leads to deficient ileal absorption of vitamin $B_{12}$. Deficiency of $B_{12}$ leads to ineffective red blood cell production in the bone marrow.

**peroxisomes** Cell organelles containing enzymes, such as catalase and oxidase, that catalyze the production and breakdown of hydrogen peroxide.

**Peutz-Jeghers syndrome** A familial syndrome consisting of mucocutaneous pigmentation and gastrointestinal polyp (usually harmartomas) formation.

**Peyer's patches** Organized lymphoid structures located on the antimesenteric border of the small intestine; contain lymphocytes and antigen-presenting cells and are important for the induction of immune responses against antigens from the intestinal lumen.

**phage** A bacterial virus that can transmit genetic material between different bacteria.

**pharmacogenetics** The study of the interrelation of an individual's hereditary constitution and response to drugs.

**pharmacokinetics** The disposition of drugs within the body in relation to their absorption, distribution, metabolism, and elimination.

**pharmacovigilance** A general term including all actions evaluating drug safety.

**pharyngeal swallow** Reflexive swallows independent of volitional control largely responsible for clearance of residual gastric refluxate and swallowed contents.

**pharyngoesophagram** Radiographic examination of the pharynx and esophagus.

**pharyngogram** Radiographic examination of the pharynx.

**pharynx** The uppermost portion of the gastrointestinal tract between the mouth and the esophagus.

**phenotype** The physical characteristics of an individual as determined by the expression of that individual's genes.

**pheromone** A chemical that, when emitted by members of a species, will affect the behavior or physiology of other members of that same species.

**phosphatase** An enzyme that catalyzes the hydrolysis of phosphate groups from substrates.

**phosphatidylcholine** A phospholipid present in cell membranes and in bile; chemically, it has a glycerol backbone. Fatty acids are esterified to the first two hydroxyl groups; a phosphate group is attached to the third hydroxyl group, yielding phosphatidic acid; the phosphate group is esterified to choline.

**phospholipase** An enzyme that hydrolyzes phospholipids at specific sites on the molecule.

**phrenic nerve** Motor nerve arising from the third, fourth, and fifth cervical segments of the spinal cord; innervates the diaphragm.

**phrygian cap** A congenital gallbladder anatomical abnormality, resulting in a conical cap shape (the traditional ancient Phrygian headgear) at the gallbladder tip.

**physiologic ileus** A normal absence of gastrointestinal contractile activity.

**pica** Persistent eating of nonnutritive substances for a period of at least 1 month, without an associated aversion to food.

**pigbel** A severe necrotizing disease of the small intestine, associated with high mortality, caused by *Clostridium perfringens* type C, and named after an illness that developed in New Guinea natives after large feasts of inadequately cooked pork.

**pili** Bacterial surface appendages involved in attachment to host cells.

**pilocarpine** A cholinergic drug that stimulates secretion of most exocrine glands, including lacrimal and salivary glands.

**pit** One of the two functional zones of the gastric unit, located superior to the gastric gland; the site of pit cells that produce the protective mucus of the gastric epithelium.

**pituitary adenylate cyclase-activating peptide (PACAP)** A neuropeptide present in the vagal nerve endings innervating the gastric mucosa.

**pituitary gland** A small endocrine organ located at the base of the brain; it governs growth, metabolism, and reproduction through the secretion of a variety of hormones.

**placebo** An inactive substance given to a participant in a research study as part of a test of the effects of another substance or treatment that is active.

**plasma membrane** The semipermeable lipid bilayer that encloses the cytoplasm of a cell.

**plexus** A network or joining together of multiple nerves, blood vessels, or lymphatic vessels.

**Plummer-Vinson syndrome** A disorder characterized by dysphagia, iron deficiency anemia, and a proximal esophageal web.

**pneumatosis** Gas within the submucosa or subserosa of the bowel wall, indicative of a loss of mucosal integrity. This may represent partial or impending perforation.

**pneumatosis coli** The presence of gas-filled cysts within the intestinal mucosa, which may occur after colonic insufflation or with colonic ischemia.

**pneumoperitoneum** The presence of air or gas in the peritoneal cavity; can be a result of disease, but can also be artificially produced (e.g., performed in a laparoscopic procedure to increase the work space available inside the abdomen).

**point mutation** A mutation that involves a single nucleotide base-pair change in the DNA sequence of a gene.

**polychlorinated biphenyls (PCBs)** Colorless and odorless chemicals, once widely used in electrical equipment; now banned from use, they remain in the environment and contaminate the food chain, primarily through waterways.

**polycystic liver disease** A disease characterized by the presence of multiple liver cysts; often occurs in association with autosomal dominant polycystic kidney disease. The condition is inherited in an autosomal dominant pattern.

**polyhydramnios** Excessive accumulation of amniotic fluid.

**poly-Ig receptor** A polymeric immunoglobulin receptor located on the basolateral surface of epithelial cells; binds polymeric immunoglobulins (IgA and IgM) and plays a critical role in transporting IgA produced by plasma cells in the lamina propria to the intestinal lumen.

**polymerase chain reaction (PCR)** A laboratory process that is used to copy nucleic acids multiple times so that there is sufficient material for analytical detection.

**polymeric** Containing complete proteins, carbohydrates, and fat rather than predigested substances.

**polymeric immunoglobulin receptor** A transmembrane protein expressed on the basolateral surface of epithelial cells lining mucous membranes; binds polymeric IgA and also IgM and transcytoses them into the lumen.

**polymorphism** A germ-line sequence alteration present in at least 1% of the given population.

**polymorphonuclear leukocyte** A white blood cell, usually neutrophilic, having a nucleus that is divided into lobes.

**polyp** An abnormal growth of tissue. Polyps are defined histologically within two broad categories, epithelial or hamartomatous. Polyps may be pedunculated (having a stalk) or sessile (flat) and the surface is often described as either smooth or lobulated.

**polypectomy** A procedure used to remove a polyp(s).

**polyposis** A condition in which numerous polyps develop in various areas of the gastrointestinal tract, usually due to a genetic defect.

**polysaccharide** A macromolecule carbohydrate consisting of more than nine monosaccharide residues joined to each other by glycosidic linkages.

**polysplenia** A syndrome consisting of multiple spleens, usually bilateral, with rudimentary and accessory splenic tissue.

**polyunsaturated fatty acids (PUFAs)** A particular class of fatty acids sharing the general characteristics of a linear carbon backbone substituted with hydrogen atoms and bearing a carboxylic group at one end of the molecule (C1). The distinguishing features of specific PUFAs are the dietary source and the presence of double bonds within the molecule.

**porphyrin** A compound with a chemical structure consisting of four pyrrole groups linked by methene bridges; the compound is pigmented and exhibits red fluorescence when exposed to ultraviolet light around 400nm (Soret band).

**porphyrinogen** A reduced form of porphyrin; not pigmented and does not exhibit fluorescence.

**porphyrin precursors** Early intermediates of the heme biosynthetic pathway (aminolevulinic acid and porphobilinogen) from which pyrrole groups are formed.

**porta hepatis (hilum)** Describing a location in the liver between the caudate and quadrate lobes that contains the portal vein, hepatic artery, hepatic nerves, hepatic ducts, and lymphatic vessels.

**portal drainage** A procedure in which venous effluent from a graft is directed into the superior mesenteric vein or portal vein, so that this blood undergoes a first-pass effect through the liver before entering the systemic circulation.

**portal hypertension** Elevation in pressure in the portal venous system. Bleeding from esophageal varices, ascites, and hepatic encephalopathy are complications of portal hypertension.

**portal tract (portal triads)** Structures composed of bile duct, hepatic artery, and portal vein, embedded within connective tissue.

**portal vein thrombosis** A thrombus clot within the portal vein.

**portal venous system** A vessel pathway beginning and ending in the capillaries.

**portoenterostomy (Kasai operation)** Surgery performed for extrahepatic biliary atresia whereby a Roux-en-Y loop of jejunum is anastomosed to the porta hepatis.

**positron emission tomography (PET)** A technique that utilizes a system especially designed to produce tomographic images of positron-emitting radionuclides.

**postcholecystectomy pain** Painful attacks that occur after removal of the gallbladder.

**postganglionic** Occurring after the ganglion.

**postganglionic neurons** Neurons of the sympathetic nervous system that have their cell bodies in peripheral ganglia and send axonal projections to the digestive tract.

**postpolypectomy syndrome** An acute syndrome composed of pain, fever, and focal colitis stemming from transmural thermal injury following the removal of a polyp with cauterization.

**postprandial** Taking place after eating.

**postprandial satiety** A sense of satiation or fullness after eating.

**posttranslational modification** The alteration of a protein after it has been synthesized. Examples include the addition of sugar chains, of phosphate, or of sulfate.

**posttraumatic diaphragmatic hernia** A rent in the diaphragm due to trauma.

**pouchitis** A clinical syndrome of abdominal cramps, frequent watery stools, urgency, incontinence, malaise, and fever in those who have had an ileal-anal anastomosis or a Koch pouch (continent ileostomy).

**pouch of Douglas** A pouch formed by a fold of peritoneum between the rectum and the uterus.

**power propulsion** A specific motility pattern that propels the intraluminal contents rapidly over extended distances in the small and large intestine.

**prebiotic** A nondigestible food ingredient that can beneficially influence the health of the host by selectively altering the enteric flora.

**predigested formula** An enteral formula consisting of amino acids and/or short peptides and/or hydrolyzed protein plus simple sugars plus minimal fat. These products are fiber-free and require less digestion by the gastrointestinal system, but still require intact intestinal absorptive function.

**prednisolone** A corticosteroid drug used to reduce inflammation in active ulcerative colitis.

**preeclampsia** A triad of hypertension, edema, and proteinuria occurring as complications in the third trimester of pregnancy.

**preganglionic** Occurring before the ganglion.

**preganglionic neurons** Neurons of the sympathetic nervous system that have their cell bodies in the spinal cord and send axonal projections to sympathetic ganglia in the periphery.

**premalignant polyp** A cell growth that has the potential of progressing to a malignancy over time.

**premeal** A term for a portion of food consumed shortly before the actual meal.

**prepro hormone** A precursor peptide containing all the hormone gene-encoded amino acids (including the signal peptide) before processing to the mature peptide.

**preterm** Descriptive term for an infant born before 37 weeks of gestation.

**prevalence** In epidemiology, the number of existing cases of a specific disease found in a defined population at one specific point in time.

**prevertebral ganglia** The celiac, superior mesenteric, and inferior mesenteric ganglia of the sympathetic nervous system located in the abdomen.

**primary bile acid** Bile acid synthesized in the hepatocyte from cholesterol.

**primary biliary cirrhosis** Autoimmune liver disease characterized by antimitochondrial antibodies, cholestatic laboratory indices, and histological features of bile duct injury, including destructive or granulomatous cholangitis (florid duct lesions).

**primary hyperparathyroidism** Inappropriately excessive parathyroid hormone production resulting in hypercalcemia.

**primary prophylaxis** The prevention of a first variceal bleed in patients with cirrhosis and varices.

**primary sclerosing cholangitis** An autoimmune liver disease, frequently associated with inflammatory bowel disease, that is characterized by cholangiographic changes of bile duct narrowing, cholestatic laboratory indices, and histological features of bile duct injury or biliary obstruction.

**probiotics** Living bacteria that colonize a host in amounts sufficient to alter intestinal microbial balance, resulting in a beneficial health effect for the host: e.g., reestablishing normal intestinal flora. Can be ingested in the form of a microbial food supplement.

**proctitis** An inflammation of the rectum, either acute or chronic; the least extensive variety of ulcerative colitis.

**proctocolitis** An inflammation that may be caused by infections of the rectum and colon; sigmoidoscopic findings extend proximally above 15 cm of the rectum.

**proctography** Radiographic evaluation of the rectum and anus.

**proctopathy** Any pathologic process involving the rectum without having a significant component of rectal inflammation.

**prodromata** A set of autonomic responses that accompany and often precede emesis or nausea.

**prodrome** Symptoms indicating the onset of a disease.

**progenitor cell** A cell with the capacity to replicate extensively, exhibit patterns of gene expression found in immature cells, and differentiate into mature cells.

**proglottid** The segment of a tapeworm that, when gravid, contains eggs.

**proglucagon-derived peptides** Secreted products of proglucagon processing, including those from the pancreas (glicentin-related pancreatic polypeptide, glucagon, and major proglucagon fragment) and those from the gut (glicentin, oxyntomodulin, and glucagon-like peptides 1 and 2).

**progressive familial intrahepatic cholestasis** Inherited disorders of neonatal cholestasis.

**prohormone** The biosynthetic precursor for a peptide/protein hormone. By cleavage of the prohormone, the mature hormone is produced.

**prohormone convertases** Enzymes responsible for the proteolytic processing (cleavage) of prohormones.

**prokinetic** Referring to agents that stimulate the movement of lumenal contents along the gastrointestinal tract.

**prolactin** A single-chain protein hormone closely related to growth hormone, secreted in the anterior pituitary. It is also synthesized and secreted by a range of other cells in the body; stimulates mammary gland development and milk production and also has many other functions.

**prolactinoma** A pituitary adenoma that secretes excessive amounts of prolactin, which may lead to the clinical symptoms of galactorrhea or amenorrhea.

**prolapse** The descent of a body part from its usual anatomical position.

**pronucleating proteins** Biliary proteins that can promote nucleation of cholesterol crystals. Examples include mucin, anionic peptide fraction, and phospholipase C.

**prostaglandins** A form of eicosanoids (biologically active lipids formed by the oxidation of 20-carbon fatty acids); produced by the cyclooxygenase pathway, they are responsible for a variety of physiologic and inflammatory reactions.

**protease inhibitors** A class of drugs employed in effective combination therapy against HIV, such as indinavir and nelfinavir. Most recently, there has been widespread use of ritonavir-boosted regimens (lower dose ritonavir in conjunction with another protease inhibitor), which exploit the fact that ritonavir is a potent inhibitor of the P450 enzyme pathway.

**protein** A macromolecular complex containing a large number of amino acid residues joined to one another via peptide bonds. Proteins may, in addition to the 20 different amino acids that they generally are made up of, contain various amino acid residues that have been modified posttranslationally by phosphorylation, hydroxylation, glycosylation, or attachment of fatty acid residues.

**protein-calorie deficiency** A condition that occurs either because of deficient protein intake (undernutrition) or because of a relative excess of calorie intake (overnutrition).

**protein kinases** Enzymes that add phosphate groups to proteins and thereby regulate their functions.

**protodifferentiated** Describing an early state of differentiation in which cells exhibit low-level expression of lineage-specific genes, but have not acquired the higher expression levels characteristic of fully differentiated cells.

**proton pump inhibitors** A class of medications that block $H^+,K^+$-ATPase ("proton pump") in the gastric parietal cell, thereby suppressing gastric acid secretion.

**proto-oncogenes** Cellular genes that are involved in the regulation of proliferation, development, and differentiation.

**provitamin A carotenoids** A subset of carotenoids, which are a class of compounds synthesized by plants and microorganisms generally containing eight isoprenoid units, that can be oxidatively metabolized to produce retinal and retinoic acid and cleavage products known as apocarotenoids.

**provocative pituitary testing** Analysis of the pituitary with specific medications previously shown to elicit a release of one or more pituitary hormones in a reproducible manner characteristic of normal or disease states.

**proximal colon** An anatomic subsite of the colorectum that includes the cecum, ascending colon, and transverse colon.

**proximal gastric vagotomy** An operation in which the vagal branches of the nerves of Laterjet are divided as they enter the lesser curvature of the stomach. This ameliorates vagally mediated gastric acid secretion from the parietal cell mass while preserving the motor branches to the antrum and the pylorus. Also called highly selective vagotomy and parietal cell vagotomy.

**pruritus** A condition or sensation of itching.

**pseudoaneurysm** Aneurysmal dilation of a peripancreatic artery produced by the local injurious effects of a pseudocyst.

**pseudocyst** A collection of fluid produced by leakage of pancreatic juice and surrounded by a capsule of fibrous and granulation tissue; a complication of pancreatitis.

**pseudomembrane** False membrane; a layer of exudate on the surface of skin or mucous membrane.

**pseudomembranous colitis** An inflammatory condition, characterized by the presence of prominent inflammatory membranes on the colonic mucosal surface. Typically present in patients with *Clostridium difficile* colitis, but can be seen as well in cases of ischemic disease and other infections of the colon.

**pseudomyxoma peritonei** A rare condition manifested by diffuse, gelatinous implants of the peritoneal cavity and omentum arising from mucinous neoplasms of the ovary or appendix.

**pseudo-obstruction** A failure of propulsive motility that cannot be explained by mechanical blockage in the gastrointestinal tract.

**pseudopolyp** A polypoid projection from the mucosa into the lumen of the colon, resulting from healing after inflammation.

**psychoform** Describing psychological symptoms suggesting psychiatric disorders that the individual does not have.

**psychosomatic** Describing bodily symptoms presumed to arise from psychological origins.

**P-type ATPase** An enzyme that utilizes ATP hydrolysis to transport cations or positively charged ions across cell membranes; "P" in this case refers to the enzymatic requirement for a high-energy covalent beta-aspartyl phosphate intermediate.

**puborectalis muscle** Sling muscle that forms part of the pelvic floor; it loops around the posterior aspect of the rectum and anchors anteriorly to the symphysis pubis. It maintains an angle between the rectum and anal canal and can be voluntarily contracted to further pinch off the rectum from the anal canal.

**pudendal nerve motor latency** A test for the integrity of the pudendal nerve; involves electrically stimulating the nerve with a finger-mounted electrode and measuring the time elapsed before the external anal sphincter contracts, as detected by electromyographic activity.

**pulse sequence** Technical parameters consisting of a set of radiofrequency pulses, magnetic gradient pulses, and the time intervals between pulses used to create the image and image contrast on magnetic resonance images (MRI).

**pulsus paradoxicus** Exaggerated decrease (greater than 20 mmHg) in inspiratory systolic blood pressure.

**purging** The elimination of undigested or partly digested food or feces by self-induced vomiting or with laxative or enema use.

**pylephlebitis** Suppurative endophlebitis of the portal venous system.

**pylethrombosis** Thrombosis of the portal venous system.

**pyloric stenosis** An acquired condition involving the thickening of the circumferential muscle of the pyloric sphincter, which results in elongation and obliteration of the pyloric channel. The most common cause of gastric outlet obstruction in children and one of the most frequent conditions requiring operation in the first month of life.

**pyloric tone** Variable levels of ongoing contraction of the musculature in the pyloric region of the stomach.

**pyloric traumamyoplasty** An alternative operative approach to pyloric stenosis involving the use of a Babcock clamp to grasp and pinch the hypertrophied pyloric muscle, creating two lateral slits on the superior and inferior edges.

**pyloroplasty** A surgical procedure that incises and divides the normal pyloric muscle, destroying it as a sphincter, and then reconstructs the pyloric channel to facilitate gastric emptying.

**pyloropyloric** Describing a reflex that is initiated in the pylorus and acts there.

**pylorus** The opening that leads from the stomach to the duodenum.

**pyoderma gangrenosum** A chronic skin ulcer sometimes complicating ulcerative colitis.

**pyogenic** Pus-forming.

**pyrrolizidine alkaloids** Plant-derived alkaloids that may cause sinusoidal obstruction syndrome.

## Q

**quantitative hepatobiliary scintigraphy** A nuclear medicine study that assesses bile flow through the biliary tract.

**quasispecies** A heterogeneous population of genetic variants of a virus found in an infected individual.

## R

**radiofrequency ablation** Ablative cancer therapy in which a probe is inserted through the skin into the tumor, with the goal of killing the tumor cells with heat.

**radionuclide** An atom with an unstable nucleus, which achieves stability by emitting excess energy in the form of gamma rays and subatomic particles (e.g., positrons). The radionuclide most commonly utilized in nuclear medicine is technetium-99m.

**radiopharmaceutical** A biologically active molecule labeled with a radionuclide.

**Ramstedt extramucosal pyloromyotomy** A standard operative approach to pyloric stenosis; involves grasping the pylorus, incising the serosa longitudinally, and spreading or dividing the thickened pyloric muscle until the mucosa is bulging between the separated halves of the pylorus.

**rapid response peptides** Molecules produced rapidly at sites of an injury which function to stimulate the repair process.

**RAST (radioallergosorbent test)** A test that measures allergen-specific immunoglobulin E in the serum of patients.

**reactive metabolites** Products resulting from the transformation of a parent compound by enzymatic reactions, principally in the liver. Most produced metabolites are nontoxic and facilitate the elimination of drugs. Occasionally, metabolites are unstable and react with cellular structures, thus causing cell damage that represents a major mechanism leading to drug-induced hepatotoxicity.

**reactive oxidant species** Compounds derived from oxygen-mediated reactions.

**receptor** A molecular structure within or on the surface of a cell that binds to a specific ligand and initiates a cellular response. The largest class of receptors is the G-protein-coupled receptor family.

**receptor-associated membrane protein-1 (receptor activity-modifying protein)** A single-membrane-spanning protein required to guide the intracellular trafficking of calcitonin receptor-like receptor to the cell membrane and to endow it with high affinity for calcitonin gene-related peptide.

**receptor component protein** An intracellular peptide important for coupling calcitonin receptor-like receptor to the G protein $G_s$/adenylate cyclase signal transduction pathway.

**Recommended Dietary Allowance (RDA)** The average daily dietary intake level that meets the nutrient requirements of nearly all (97–98%) healthy persons of a specific sex, age, life stage, or physiological condition (such as pregnancy or lactation).

**rectal neck** Another term for the anal canal.

**rectal procidentia** A circumferential full-thickness intussusception of the rectum in which the lead point of the intussusception descends through the anal canal.

**rectoanal reflex** A reflex relaxation of contractile tone in the internal anal sphincter, evoked by distension of the rectum.

**rectopexy** Fixation by suture or prosthetic mesh of the mobilized rectum to the presacral fascia (to prevent rectal intussusception).

**rectum** The most distal portion of the colon.

**recurrent abdominal pain** Paroxysmal abdominal pain that persists for greater than 3 months' duration and affects normal activity.

**recurrent pancreatitis** Recurrent inflammation of the pancreas.

**reflux** Backward flow or movement, as in reflux of contents from the stomach into the esophagus.

**refractory celiac disease** Celiac disease that is not responsive to 6 months of a strict gluten-free diet.

**regional blocking procedure** A method of injecting local anesthesia under the skin, but around the nerves that are supplied to a specific area.

**regional enteritis** Inflammation of a region of intestine.

**regression** The process of return of liver parenchyma toward a normal histologic appearance, as in regression of cirrhosis.

**Reiter's syndrome** A chronic form of inflammatory arthritis characterized by the inflammation of the joints, the eyes, and the genital, urinary, or gastrointestinal system.

**rejection** The immune reaction of a transplant recipient to foreign tissues (antigens) after allograft transplantation, with production of antibodies and ultimate destruction of the transplanted organ.

**renal** Relating to or affecting the kidney function.

**renal failure** Loss of kidney function, either acute or chronic, that results in azotemia and syndrome of uremia.

**rennin-angiotensin-aldosterone system** The vasoactive system that causes renal vasoconstriction and retention of sodium and water.

**reperfusion** Restoration of blood flow following a period of ischemia.

**resistant starch** The portion of ingested starch that escapes digestion in the small intestine.

**restitution** The process by which surviving cells at the edge of a wound migrate across the denuded area to reestablish epithelial continuity. This process is not dependent on cell proliferation.

**RET** A gene that encodes for a receptor tyrosine kinase.

**retching** A strong involuntary effort to vomit.

**reticulin stain** A histochemical stain that highlights the delicate collagen fibers.

**retinoids** Naturally occurring compounds with vitamin A activity and synthetic analogues with or without vitamin A activity. These include analogues such as isotretinoin (13-*cis*-retinoic acid) that are used medically to treat acne.

**retinopathy** Retinal changes occurring in diabetes mellitus, marked by microaneurysms, exudates, and hemorrhages, and sometimes by neovascularization.

**retinyl esters** Fatty acid conjugates of retinol that are the primary storage form of vitamin A in animal tissues.

**retroflexing** The positioning of the tip of an endoscope so that it is turned around 180° to provide a backward view.

**retroperitoneum** The space behind the peritoneal cavity and anterior to the muscles and bones of the back, the site of the blood vessels, nerves, and lymph nodes associated with the abdominal viscera.

**reverse cholesterol transport** The process through which high-density lipoprotein acquires cholesterol from peripheral cells and transports and delivers it to the liver for secretion into bile or for use in the synthesis of bile salts.

**rheumatoid factor** An autoantibody directed against immune globulin that is present in rheumatoid arthritis.

**rhythmic phasic contractions** Regularly occurring contractions of colon musculature that cause mixing and slow net distal propulsion of digesta.

**ribavirin** A guanosine analogue that has antiviral and immunomodulatory effects; increases the sustained viral response rate of interferon when the combination is used to treat patients with chronic hepatitis C virus.

**rickets** A disease caused by vitamin D or phosphate deficiency during childhood; it is characterized by lack of growth plate fusion and bowing of the long bones, with defective bone matrix mineralization.

**rifaximin** An unlicensed and poorly absorbed antimicrobial agent with activity against enteric bacterial pathogens, effective in reducing the duration of diarrhea when used therapeutically.

**RNA editing** A form of posttranscriptional modification in which the nucleotide sequence of the transcript is modified from that encoded in the genome.

**RNA polymerase** The viral enzyme needed to replicate the double-stranded RNA viral genome in the mammalian host.

**Rome II criteria** The consensus criteria developed to diagnose sphincter of Oddi dysfunction.

**Rotor syndrome** A genetic disorder of unclear etiology characterized by conjugated hyperbilirubinemia.

**Roux-en-Y** A surgical anastomosis between the common bile duct and the jejunum.

## S

**saccular aneurysm** An eccentrically shaped aneurysm.

**salivary hypofunction** The objective diminution of salivary output.

**salvage therapy** Antimicrobial regimens designed to be used after the failure of first-line therapies.

**sampling reflex** A process in which internal and external anal sphincters spontaneously relax for brief periods, allowing the contents of the rectum to be exposed to the sensory receptors in the upper anal canal.

***Sapovirus*** Recently adopted name to designate the genus of the viral family, Caliciviridae; previously called Sapporo-like viruses or classic caliciviruses.

**sarcopenia** Age-dependent loss of skeletal muscle fibers and their replacement by intramuscular fat in the elderly, leading to reduced strength of gait and predisposition to falls.

**saturation** A fraction or percentage describing the cholesterol concentration of a bile sample relative to its equilibrium solubility (at saturation). Mathematically, it is the cholesterol concentration divided by the equilibrium solubility in the sample, or that predicted to hold for a sample based on studies of model systems simulating bile.

**savary dilator** A flexible polyvinyl dilator with a central guide-wire lumen. Used to dilate esophageal strictures.

**Schatzki ring** A fibrous ring of tissue at the esophago-gastric mucosal junction that can cause dysphagia.

**scintigraphy** The process of obtaining images with a gamma camera.

**sclerosant** An agent (usually liquid) that, when injected, causes thickening and fibrosis in tissue. Used in upper gastrointestinal endoscopy to control bleeding from a vessel.

**sclerosing cholangitis** Slowly progressive inflammatory scarring of bile ducts, leading eventually to liver failure; may occur in association with ulcerative colitis.

**sclerotherapy** The injection of a highly irritating substance into a blood vessel, which causes a clot to form.

**scolex** The head of a tapeworm.

**secondary biliary cirrhosis** End-stage liver disease due to obstruction of extrahepatic bile ducts, which leads to cholestasis and proliferation of small bile ducts and fibrosis.

**secondary prophylaxis** Prevention of recurrent variceal hemorrhage in a patient who suffers a first episode of variceal bleeding.

**secondary spread** Transmission of infection from an index case to close contacts. In foodborne diseases, this usually is via fecal-oral contamination of foodstuffs.

**second messenger** An intracellular mediator produced in response to the binding of agonist to its specific receptor. These signaling molecules activate effector molecules either directly or via activation of protein kinases; e.g., cyclic AMP.

**secretagogue** A substance, such as a hormone or paracrine signal, that stimulates secretion.

**secretin** A gastrointestinal peptide hormone that stimulates bicarbonate and fluid secretion from pancreatic ducts.

**secretion** The active or passive movement of a substance from the blood side of the gut (serosal) to the lumen of the gut (mucosal side).

**secretomotor neurons** The neurons in the enteric nervous system, which innervate the intestinal crypts of Lieberkuhn to evoke the secretion of water, electrolytes, and mucus.

**secretory component** The external domain of the polymeric immunoglobulin receptor; remains attached to the secreted antibody.

**secretory diarrhea** A diarrheal illness that is driven by the active secretion of salt and water by intestinal epithelial cells.

**secretory granule** A membrane-bound vesicle containing condensed secretory material.

**sectoral bile ducts** Bile ducts formed by the merging of segmental bile ducts.

**segmental bile ducts** Bile ducts draining segments of the liver.

**segmentation** A specific pattern of small intestinal motility that starts with the ingestion of a meal and accomplishes mixing of the contents in the lumen; also called digestive motility.

**senescence** An age-dependent decline in physiological capacities and anatomic integrity that proceeds throughout adulthood.

**septum** The linear fibrous array that subdivides the parenchyma. Septa are actually planes when seen in three dimensions.

**sequestration** Retention of formed elements of the blood as they pass through the spleen, often leading to their destruction or to enlargement of the spleen.

**serine proteases** A family of proteolytic enzymes with a common mechanism of action involving a serine residue at the active site.

**serine/threonine kinase 11** A gene that is mutated in patients with Peutz-Jeghers syndrome.

**serogrouping** The categorization of bacteria into groups with similar carbohydrate-based surface antigens. Tests are done by agglutination with defined antisera.

**serosal eosinophilic gastroenteritis** Eosinophilic infiltration extending into the serosal layer of the gastrointestinal tract, resulting in symptoms such as abdominal distension and pain.

**serotonin** An amine (5-hydroxytryptamine) synthesized from the amino acid L-tryptophan; has various important biological effects.

**serous cells** Salivary gland secretory cells that produce a watery saliva rich in proteins with enzymatic or antimicrobial functions.

**serpin (serine proteinase inhibitors)** A family of circulating molecules that share structural similarities yet carry out diverse physiological functions in the body.

**serum amylase** Pancreatic amylase in the serum; this serves as a marker of acinar cell damage, i.e., pancreatitis.

**shock** A marked decrease in tissue perfusion, usually associated with a fall in blood pressure that deprives vital tissues of oxygen.

**short bowel syndrome** A spectrum of intestinal malabsorption that occurs after major resection of the small intestine.

**short-chain fatty acids** Organic acids produced by anaerobic fermentation of undigested carbohydrates within the colonic lumen.

**short tau inversion recovery (STIR)** Magnetic resonance pulse sequence in which T1- and T2-dependent contrasts are additive and signal from fat is suppressed.

**side-to-side portacaval shunt** A surgically created shunt promoting flow from the portal vein into the inferior vena cava, bypassing an occluded hepatic outflow tract.

**sigmoidoscopy** A technique for obtaining intralumenal visualization of the rectum, sigmoid, and, usually, left colon, utilizing a fiber-optic endoscope.

**signaling** A sequential process that results in conversion of an extracellular event into an intracellular message.

**signal transducers and activators of transcription (Stat)** Proteins (Stat 1, Stat 4, and Stat 6) involved in Th1 and Th2 differentiation.

**signal transduction mechanisms** The chemical and mechanical process by which a peptide binding to its receptor on the cell membrane results in some physiologic effect within a cell.

**silent celiac disease** Asymptomatic celiac disease in patients with an abnormal intestinal biopsy.

**silver stain** A special stain used to detect fungal organisms not seen by regular microscopy.

**sinusoid** The channel between the hepatic cords.

**sinusoidal obstruction syndrome** A nonthrombotic obstruction of the hepatic circulation with subsequent centrilobular sinusoidal fibrosis and, often, fibrotic obliteration of hepatic venules. Formerly known as hepatic venoocclusive disease.

**Sister Mary Joseph's nodule** A periumbilical mass that may contain lymph node metastases from a peritoneal source of malignancy.

**situs inversus viscerum** A condition in which the viscera are transposed in the abdominal cavity, with the liver on the left side and the stomach and spleen on the right.

**Sitzmarker colon transit test** A technique using radiopaque markers to calculate segmental and colon transit by counting markers on abdominal "radiographs".

**Sjögren's syndrome** An immunological disorder causing mucosal and conjunctival dryness from progressive destruction of exocrine glands and associated with other autoimmune phenomena.

**skin-prick test** A procedure in which a small needle or lancet is pressed through a commercial extract of a food into the epidermis. The presence of immunoglobulin E against the food tested results in a measurable wheal-and-flare reaction.

**sliding hiatal hernia** A defect in which the gastroesophageal junction and some portion of the stomach are displaced above the diaphragm, but the stomach axis remains unchanged.

**slow waves** Periodic spontaneous depolarization of smooth muscle cells that regulate the maximum frequency, direction of propagation, and timing of occurrence of contractions on receiving an excitatory signal from the motor neurons.

**small bowel bacterial overgrowth** Excess bacterial counts in any area of the small bowel, usually greater than $10^{10}$ colony-forming units/ml.

**small bowel series** Radiographic examination of the small bowel.

**small intestine** The anatomical structure that consists of the duodenum, jejunum, and ileum, where most digestion and absorption of nutrients takes place.

**sodium taurocholate** A bile salt that induces pancreatitis when injected retrograde into the pancreatic duct.

**soiling** The involuntary seepage of feces that is frequently associated with fecal impaction and which reflects staining of the underwear.

**solitary rectal ulcer syndrome** A condition that is clinically characterized by a disturbance of defecation, blood and mucus per rectum, and abnormalities of the rectal wall ranging from erythema to polyp formation to ulceration.

**solubility product** The mathematical product of the concentration of the anion times the concentration of the cation of a salt that has a low solubility in water. When the solubility product of a salt is exceeded, the solution is supersaturated, and the salt can potentially precipitate from solution.

**somatic mutation** An acquired mutation in a non-germ-line tissue.

**somatization disorder** A psychiatric illness that occurs predominantly in women, characterized by multiple physical complaints throughout the body's organ system without medical explanation.

**somatoform** Describing physical symptoms suggesting a medical basis but without medical explanation.

**somatostatin** A peptide hormone produced in the stomach; inhibits gastric acid secretion and gastrin secretion.

**sonic hedgehog** One member of a family of signaling proteins originally described in *Drosophila*. Sonic and Indian hedgehog proteins are key regulators of gastrointestinal morphogenesis.

**space of Disse** A virtual space located between the sinusoidal endothelial lining and the parenchymal hepatocyte population.

**spectral Doppler** A display of the constituent components of the Doppler signal over time.

**sphincter** A ringlike band of muscle fibers that constricts a passage or closes a natural orifice. The muscle may be skeletal as in the upper esophageal and external anal sphincters, or smooth as in the lower esophageal and internal anal sphincters.

**sphincter ablation** The surgical removal of a sphincter.

**sphincterotomy** An incision or division of a sphincter, especially the sphincter of Oddi.

**sphincter of Oddi** Muscular region surrounding the distal ends of the common bile duct and pancreatic duct as they enter the duodenum. When constricted, this sphincter prevents flow of bile and pancreatic juice into the duodenum and restricts reflux of duodenal contents back into the bile and pancreatic ducts.

**spinal anesthesia** A technique in which local anesthetics are placed within the fluid-filled sack around the spinal cord, blocking nerve impulses.

**splanchnic** Mesenteric or intestinal in origin.

**splenic flexure** The section of the colon representing the transition from the transverse colon to the left colon, typically located in the left upper quadrant of the abdomen, inferior to the spleen.

**splenomegaly** An abnormal increase in the size of the spleen.

**spontaneous bacterial peritonitis** A primary infection of ascitic fluid in patients with advanced liver disease.

**sprue** See TROPICAL SPRUE.

**squamous** Describing a flat type of epithelium classified by a type of cell whose width is much larger than its height.

**stable isotope** An isotope containing more or fewer neutrons in the nucleus than those observed in the most abundant form of the element.

**steatorrhea** The presence of significant undigested fat in the stool; a marker of inadequate or incomplete digestion of fat.

**steatosis** The accumulation of fat within the cells of an organ, such as the liver, resulting in diminished functioning.

**stellate cells** Facultative fibroblasts residing in the subendothelial space of sinusoids.

**stem cell** A cell with the capacity to produce differentiated cells of more than one lineage or multiple lineages without losing the capacity for self-renewal.

**stenosis** An area of narrowing, especially a pathologic narrowing or stricture of a duct or passageway that may be either acquired, e.g., by radiation injury to the esophagus, or congenital, e.g., esophageal stenosis.

**stent** A hollow plastic tube inserted into a narrowing in a tract of the body as a nonoperative method of widening the diameter of the passage.

**stigmata** Endoscopically visible signs of recent hemorrhage such as active bleeding, adherent clot, or visible vessel.

**stomach** The part of the gastrointestinal tract that lies between the esophagus and the duodenum.

**stomach polyp** A raised mass in the inner lining of the stomach that protrudes into the lumen.

**stool osmotic gap** The difference between luminal osmolality and luminal content osmolality, calculated by electrolyte measurements.

**stress** Adaptive physiological response to a real or perceived threat to homeostasis; a natural system to protect the individual and restore equilibrium to the system, but also can have harmful effects over time.

**stressor** Any external or internal physical, biological, environmental, or situational factor that can represent an actual or perceived threat to homeostasis.

**striated ducts** Intralobular salivary ducts with a striated appearance due to membrane infoldings and aligned mitochondria; active in electrolyte secretion and absorption.

**stricture** A narrowing or stenosis of a hollow structure, usually consisting of cicatricial contracture or deposition of abnormal tissue.

**strobilation** The process by which a tapeworm grows in an anterior to posterior direction.

**S-type enteric neuron** A neuron identified by specialized electrical behavior that includes elevated excitability and the universal presence of fast excitatory postsynaptic potentials and Dogiel Type I neuron morphology.

**subconfluent** Describing cells at low density that have not yet formed a continuous layer.

**subfulminant liver failure** Acute hepatitis accompanied by encephalopathy that begins after 2 weeks, but within 8–12 weeks from the presentation of jaundice.

**subjective global assessment** A comprehensive assessment of nutritional status using both objective and subjective clinical findings.

**submucosal tumor** A growth of tissue in the intestinal wall that originates from the submucosa, from the muscularis propria, or from extrinsic compression by adjacent structures.

**submucous plexus** (Meissner's plexus) A network of nerves and small ganglia found in the submucosa of the intestine. It is composed of outer and inner layers and transmits secretomotor and vasodilator stimuli to the mucosa.

**sucralfate** A basic aluminum salt of sucrose octasulfate; it protects mucosal integrity locally without substantially altering gastric pH.

**superantigen** A protein antigen that differs from a conventional antigen in several aspects, especially its ability to elicit a massive cytokine response, typical of what occurs in Kawasaki syndrome.

**sustained stress** Chronically ongoing stressful situations in a person's life, e.g., marital problems, death of a family member, change in role in life, change in job, significant financial loss.

**sympathetic nervous system** A portion of the nervous system that responds automatically to stresses on the body, such as perceived danger, physical exertion, temperature change, and hemorrhage.

**synbiotic** Describing a mixture of prebiotic and probiotic elements.

**synchronous neoplasia** Tumors (adenomas, adenocarcinomas, or a combination of both) that are diagnosed at the same point in time.

**syncytium** A group of cells that behave as a unit due to some form of coupling between cells (electrical coupling in smooth muscles).

**systemic drainage** A procedure in which venous effluent from a graft is directed to the systemic circulation via the vena cava, so that it does not first filter through the liver.

**systemic inflammatory response** A systemic reaction occurring after a variety of insults, including infection, trauma, ischemia, or immune-mediated organ injury; involves one or more of the following: alteration in body temperature; increased heart rate; rapid deep breathing; change in white blood cell count.

## T

**tachygastria** Faster than the normal (three per minute) electrical slow-wave activity generated by the smooth muscle layer of the stomach.

**tachykinins** A family of neuropeptides sharing the same carboxyl-terminal amino acid sequence comprising the molecular center of biological activity of each peptide. The mammalian tachykinins include substance P and neurokinin A and B.

**tacrolimus** A potent drug that works similarly to cyclosporin by blocking T-cell reactivity to interleukin-1 (IL-1) and therefore T-cell production of IL-2.

**taenia coli** Three strips of longitudinal smooth muscle spaced equidistantly around the circumference of the colon.

**targeted homologous recombination** A genetic technique whereby a targeted or defective gene can be cleaved from DNA and replaced by a normal form of the gene.

**taste bud** A cluster of 80-150 specialized epithelial cells; responsible for the initial events of taste reception.

**T cell** A thymus-derived immune cell essential for cell-mediated immune responses; recognizes only foreign protein/antigen in the context of major histocompatibility antigens.

**T cell receptors** Complexes on the surface of T lymphocytes that are responsible for the recognition of specific antigen/major histocompatibility glycoprotein complexes.

**telangiectasia** A vascular abnormality of small veins, arteries, and capillaries of the gastrointestinal tract. The abnormal vessels can become dilated, thin, and fragile, causing gastrointestinal bleeding. Telangiectasias are most commonly seen in the stomach and small intestine and tend to be multiple rather than single.

**tenesmus** A painful spasm of the anal sphincter, causing an urgent desire to evacuate the bowel or bladder and involuntary straining, with the passage of little fecal matter or urine.

**tensostat** A computerized pump that applies fixed tension levels to the wall of hollow viscera.

**term newborn** An infant born at or after 37 weeks of gestation.

**T helper cells** Specialized T cells (T lymphocytes) that play a key role in the immune response. **Th1** cells participate in cell-mediated immunity; **Th2** cells are essential for antibody-mediated immunity.

**thoracoabdominal aneurysm** An aneurysm involving the suprarenal mesenteric vessels; may also involve the descending thoracic aorta in the chest.

**thrombocytopenia** A reduction in the number of platelets in the circulating blood.

**thrombosis** Partial or complete obstruction of a vessel with a clot originating at the site of the obstruction.

**thromboxane** A product of cyclooxygenase metabolism in platelets; serum concentrations of thromboxane correlate with platelet activity.

**tight junction** A complex of proteins near the apical side of epithelial cells, acting as a barrier to the movement of molecules between the cells.

**T lymphocyte** See T CELL.

**TNM staging** A universal cancer classification system that is based on tumor extent (T), lymph node status (N), and the presence or absence of distant metastases (M); provides a standardized measure for planning treatment and predicting prognosis.

**tolerable upper intake level** The highest level of chronic, usual daily nutrient intake that is likely to pose no risk of adverse health effects to almost everyone in the population.

**Toll-like receptors** Transmembrane surface receptors involved in the detection and recognition of pathogen structural determinants.

**tonicity** A measure of the number of osmotic particles within a fluid. Isotonicity refers to a similar number of particles in an intravenous solution and in the blood plasma. A hypertonic solution has a higher concentration of a solute than is found in blood.

**TORCH infection** Toxoplasmosis, rubella, cytomegalovirus, and herpesvirus congenital infections associated with fetal malformations.

**total energy expenditure** A set of equations that estimate the energy expenditure needed to maintain current body weight and activity levels.

**total parenteral nutrition** The provision of complete nutrition via the intravenous route.

**toxic megacolon** An acute distension of the large bowel, which may cause colonic perforation and usually requires urgent surgery.

**toxins A/B** High-molecular-weight protein exotoxins released from toxigenic strains of *Clostridium difficile*. The genes for toxins A and B have been cloned and found to be separated by only 1.2 kb on the *C. difficile* chromosome.

**transarterial embolization** Catheterization of the hepatic artery via the femoral artery and using various modalities to selectively embolize the bleeding vessel.

**transcellular transport** Vectorial transport of material through the cytosol of epithelial cells; results in net movement of material between the two compartments faced by epithelial cells.

**transcobalamin** A cobalamin-binding nonglycosylated protein that is produced by all epithelial cells, circulates in the blood, and delivers cobalamin to the tissues of mammals.

**transcription factor** An intracellular protein that regulates gene transcription.

**transcript messenger RNA** The required intermediate between the genetically encoded sequence and protein product.

**transepithelial transport** The movement of nutrients across the intestinal mucosal layer, which is made up of epithelial cells joined together by tight junctions.

**transesophageal echocardiography** Examination of the heart with an ultrasound probe placed through the esophagus.

**transfected** Describing cells with artificially introduced genes in their chromosomes.

**transferrin (Tf)** An iron-binding molecule found in several compartments in the body. Circulating transferrin carries iron to and from body tissues and may apprise intestinal cells about body iron status.

**transferrin receptor** A protein involved in endocytosis of diferric transferrin; binds the HFE molecule.

**transferrin receptor 2** Recently discovered protein expressed predominantly on hepatocytes; also involved in endocytosis of diferric transferrin, but it is uncertain if this receptor binds HFE.

**transjugular intrahepatic portosystemic shunt** Placement of a self-expanding metal mesh stent between the hepatic vein and a branch of the portal vein via angiographic catheters inserted through a jugular vein.

**translational control** The regulation of protein synthesis at the level where the mRNA sequence is translated into the amino acid sequence on the ribosome.

**transmembrane proteins** Portions of the polypeptide chain, usually lipophilic in nature; capable of traversing the cell membrane lipid bilayer, often multiple times.

**transphosphorylation** A chemical reaction that involves the transfer of a phosphoric group from one compound to another.

**transplantation** The transfer of living organs or tissue from one individual to another.

**transport by passive diffusion** A process by which a solute moves from one side of the membrane to the other without the need for a specialized transporting system.

**traveler's diarrhea** A term for infectious diarrhea acquired while traveling outside own's own country or region, associated with the consumption of unfamilar foods and the general effects of long-distance travel.

**trefoil factors** A family of acid- and enzyme-resistant peptides secreted by the mucin-secreting cells in the gastrointestinal tract; they protect the gastrointestinal mucosa and assist ulcer healing.

**trematode** A parasitic nonsegmented flatworm of the class Trematoda in the phylum Platyhelminthes; also known as a fluke.

**triglyceride** A fat in which fatty acids are esterified to each of the three alcoholic groups.

**trimester** One of three portions of a pregnancy in time; the first, second, and third trimesters roughly correspond to months 1–3, 4–6, and 6–9.

***Tropheryma whipplei*** The bacterium causing Whipple's disease.

**trophozoite** The vegetative or growing form of an organism, used to describe an asexual stage of a protozoan organism.

**tropical sprue** A disorder of unknown cause affecting people living in tropical and subtropical areas who develop abnormalities of the lining of the small intestine, leading to malabsorption and deficiencies of many nutrients.

**tropic hormones** A class of hormones that play a role in stimulating bowel adaptation by encouraging intestinal villous growth and in regulating intestinal motility.

**Trousseau's sign (syndrome)** Recurrent or migratory superficial thrombophlebitis that may be an early manifestation of abdominal cancer or other systemic illnesses.

**true aneurysm** A term for the type of aneurysm that involves all three layers of arterial wall.

**truncal obesity** Waist/hip ratio (waist circumference divided by hip circumference) equal to or greater than 0.85 and 0.90 in women and men, respectively.

**truncal vagotomy** Division and resection of part of the vagus nerves as they exit the esophageal hiatus; commonly

performed to prevent vagally mediated gastric acid secretion.

*Trypanosoma cruzi* The blood-borne protozoan parasite responsible for Chagas' disease.

trypsin A pancreatic digestive enzyme whose premature activation within the pancreas is a common feature of various models of pancreatitis.

trypsin activation peptide The amino-terminal portion of trypsinogen that is cleaved to release trypsin.

trypsin inhibitor protein A pancreatic secretory protein that inhibits the action of trypsin and functions as a protective mechanism to prevent inadvertent activation of digestive enzymes within the pancreas.

trypsinogen A pancreatic digestive enzyme that, once activated, has the capacity to activate all the other pancreatic digestive enzymes.

T-tube A synthetic tube in the shape of a "T" whose transverse limb stents the site of an incision in the bile duct and whose vertical limb is brought through that incision and through the abdominal wall. Biliary anatomy may be defined by the injection of contrast material through the vertical arm and stones may be manipulated through it.

tumor An abnormal collection of cells that form a mass or polyp; in the lay community, at times assumed to be equivalent to "cancer," although tumors can be either malignant (i.e., cancerous) or benign (noncancerous).

tumor necrosis factor alpha (TNFα) A cytokine that is important in the inflammation seen in Crohn's disease and rheumatoid arthritis secondary to its effect on T helper 1 immune responses.

tumor necrosis factor beta (TNFβ) A cytokine released from macrophages that induces biological effects, including cytotoxicity, on other cells.

tumor suppressor gene A genetic sequence encoding a product that normally suppresses tumor formation (anti-oncogene); inactivation by mutation or transcriptional silencing contributes to tumor formation.

type III secretion apparatus A macromolecular structure on the surface of some gram-negative pathogenic bacteria; required for the direct translocation of bacterial virulence proteins into the cytosol of the host cell.

typhoid fever A syndrome characterized by high fevers, chills, abdominal pain, bacteremia, and metastatic seeding of organs, bones, and other structures with bacteria. Diarrhea may or may not be present. The principal agent is *Salmonella enterica*, serotypes Typhi and Paratyphi; several rarer NTS serotypes have been occasionally implicated as well. Prior to the availability of antibiotics, this disease was frequently fatal. Also called enteric fever.

## U

UC See ULCERATIVE COLITIS.

ulcer A break in the lining of the stomach, duodenum, or esophagus where hydrochloric acid and pepsin are present. Ulcers formed in the stomach are known as gastric or stomach ulcers; ulcers formed in the first part of the small intestine are known as duodenal ulcers. The exact endoscopic definition of an ulcer remains controversial, with disagreement on the lesion size (usually 3–5 mm), but most agree perception of lesion depth is necessary.

ulcerative colitis (UC) A condition of chronic idiopathic inflammatory colitis, characterized by ongoing superficial inflammation extending to a varying degree in a continuous fashion from the rectum to the proximal colon.

ultrastructural Visible under the electron microscope.

uncinate process The portion of the pancreas that lies between the descending aorta posteriorly and the superior mesenteric artery anteriorly.

undernutrition A condition defined by one or more of the following conditions: unintentional loss of more than 10% of usual body weight in the preceding 3 months; body weight less than 90% of ideal for height; body mass index less than 18.5.

uniparental disomy Two exact copies of the same chromosome or gene cluster from one parent.

unstirred water layer A region consisting of a series of lamellae of water, progressively less and less stirred as one moves from the bulk phase in the intestinal lumen to the brush border membrane.

upper arm anthropometry An indirect means of measuring one's fat and muscle mass using triceps and subscapular skin folds (indexes of body fat) and the mid-upper arm circumference (an index of skeletal muscle).

upper esophageal sphincter The muscular valve at the upper end of the esophagus.

upper gastrointestinal Pertaining to the esophagus, stomach, or duodenum.

upper gastrointestinal bleeding Blood loss from any portion of the digestive tract proximal to the ligament of Trietz (fourth portion of the duodenum).

urease Enzyme produced by *Helicobacter pylori*; it converts urea into ammonia and assists in survival of the bacteria in the stomach. Utilized by various tests to detect the presence of *H. pylori*.

urease breath test A method to test for *Helicobacter pylori*. A carbon isotope-labeled urea compound is swallowed; in the presence of *H. pylori* urease, the compound is metabolized into isotopic carbon dioxide ($^{13}C$ or $^{14}C$) that is detected in exhaled breath.

ureolysis Cleavage of urea to carbon dioxide and ammonia by bacterial enzymes.

uveitis Inflammation of the anterior chamber of the eye, sometimes complicating active ulcerative colitis.

## V

VACTERL An acronym for abnormalities of vertebrae, anus, cardiovascular tree, trachea, esophagus, renal system, and limb buds; condition associated with administration of sex steroids during early pregnancy.

**vagal** Pertaining to the vagus nerve of the parasympathetic nervous system.

**vagotomy** Surgical procedure in which the vagus nerves are cut, to reduce innervation of the stomach.

**vagus nerve** Cranial nerve X; the paired vagus nerves provide parasympathetic innervation to the heart, lungs, and gastrointestinal tract, including the pancreas.

**valves of Houston** The three or four crescentic transverse folds of the rectum.

**variceal band ligation** Endoscopic placement of a rubber ligature around a varix.

**varices** (*sing.* **varix**) Abnormally swollen or dilated blood vessels in the esophagus and/or stomach related to portal hypertension.

**vascular malformation** A result of abnormal development of vascular structures. They are subclassified based on their predominant channel type (capillary, venous, lymphatic, arteriovenous, etc.).

**vasoactive intestinal (poly)peptide (VIP)** A polypeptide from the small intestine; it induces systemic vasodilation, hypotension, increased cardiac output, respiratory stimulation, and hyperglycemia.

**vasoactive intestinal peptide (VIP) family** VIP and peptides homologous to VIP, including secretin, glucagon, PHM (a 27-amino-acid peptide having N-terminal histidine and C-terminal methionine), pituitary adenylate cyclase-activating peptide (of either 27 or 38 amino acids in length), gastric inhibitory peptide, growth hormone-releasing factor, and helodermin.

**vasoconstriction** The process of blood vessels closing down or constricting, to limit the amount of blood flowing through them.

**vasodilator** An agent (such as a nerve or a drug) that causes dilation of a blood vessel.

**vasopressin** An antidiuretic hormone that is secreted by the posterior pituitary and that increases in the blood when subjects report nausea.

**venoocclusive disease** Hepatic venous outflow obstruction that occurs in patients undergoing bone marrow transplantation, radiation therapy, liver transplantation, or ingestion of alkaloid toxins; the result of occlusion of hepatic sinusoids and small venules.

**vermiform** Wormlike, a term often used to describe the appendix.

**very-low-density lipoprotein (VLDL)** A large lipoprotein particle synthesized in the liver and small intestine containing complex lipid for export. VLDLs are the major lipoproteins secreted by the liver and contain apolipoprotein B100 as the predominant protein.

**vesicle** Structure of lipids dispersed in an aqueous solution, usually surrounded by a phospholipid bilayer.

**villi** (*sing.* **villus**) Finger-like projections of mucosa covered with differentiating epithelial cells that increase the absorptive area of the intestine.

**VIPoma** An endocrine tumor, usually of the pancreas, that produces vasoactive intestinal peptide.

**viral hepatitis** Liver inflammation caused by viral infection.

**Virchow's node** A lymph node located at the terminus of the thoracic duct in the left supraclavicular region that may contain lymph node metastases from distant primary sites via the retroperitoneal and postmediastinal lymph channels.

**virtual colonoscopy** Three-dimensional images of the colon, simulating an endoscopic view, created using information obtained from a computer tomography scan.

**visceral hypersensitivity** Increased visceral perception; perceived as pain.

**viscus** The tubular portion of the gastrointestinal tract.

**vitamer** The active analogue and isomer of a vitamin.

**vitamin** Organic substances necessary in minute quantities to maintain normal metabolism, usually working as cofactors by regulating biochemical processes.

**vitamin A** Fat-soluble substances that possess the biological properties of the prototypic vitamin A compound, all-*trans*-retinol, which is an unsaturated isoprenoid alcohol with five conjugated all-*trans* double bonds. Other important naturally occurring examples include retinal and retinyl esters. Dietary retinol and retinyl esters are referred to as preformed vitamin A.

**vitamin $B_{12}$** Micronutrient that belongs to the family of corrinoids; present in animal-derived alimentary tracts and synthesized only by microorganisms. $B_{12}$ corresponds to several vitamers named cobalamins.

**volatile sulfide compounds** Compounds such as hydrogen sulfide, methyl mercaptan, and dimethyl sulfide that are the main cause of halitosis and that are produced from sulfur-containing amino acids by bacterial putrefaction.

**volvulus** Abnormal twisting of a segment of the stomach or intestine on itself in the longitudinal axis, often resulting in bowel obstruction.

**vomeronasal organ** Sensory organ specialized to detect pheromones in certain animals.

**$VPAC_1$ and $VPAC_2$** Specific, high-affinity membrane receptors for vasoactive intestinal peptide; both are $G_s$-coupled receptors spanning the plasma membrane seven times.

## W

**warm ischemia** Interruption of the inflow of blood and oxygen during liver surgery, shock, and trauma; occurs at normothermic (body) temperature.

**WDHA** A syndrome of watery diarrhea, hypokalemia, and achlorhydria, associated with vasoactive intestinal peptide-secreting tumors (VIPomas); also known as pancreatic cholera or Verner-Morrison syndrome.

**web** A thin membrane of tissue attached to the wall of the intestine and causing intestinal blockage.

**wedge biopsy** A surgical procedure to obtain liver tissue by excision.

**Whipple operation** A major surgical procedure in which the head of the pancreas, the duodenum, and the lower end of the common bile duct are all removed, usually because of cancer of the head of the pancreas.

**Whipple's disease** A rare chronic disease; symptoms are weight loss, arthralgia, diarrhea, and abdominal pain.

**whole-body neutron activation** *In vivo* neutron activation analysis that uses a neutron beam to activate body nitrogen, which can then be measured in a whole-body radiation counter.

**windsock** A term for a type of partially obstructing duodenal web that balloons into the more distal duodenum like an internal diverticulum.

## X

**xanthelasma** Yellow plaques on the eyelids or around the eyes.

**xanthoma** A yellow nodule of the skin, composed of lipid-laden histiocytes.

**xenograft** Transplantation of cells from a different species with incompatible major histocompatibility complex antigens.

**xenolytic breath test** A breath test based on formation of hydrogen or labeled carbon dioxide from an ingested substrate by bacterial enzymes.

**xerostomia** The subjective feeling of dryness of the mouth, usually associated with diminished or arrested salivary secretion.

## Y

**YMDD mutation** A mutation in the hepatitis B virus polymerase gene in which methionine is replaced by serine; associated with lamivudine therapy and drug resistance.

## Z

**Zenker's diverticulum** A pharyngeal out-pouching above the upper esophageal sphincter as the result of weakness in the posterior pharyngeal wall.

**zeta-interacting proteins** A family of metal transporters with a high avidity for zinc.

**zinc finger motifs** Structural domains associated with specific DNA-protein transcription factor interactions that are dependent on zinc for structural integrity.

**Zollinger-Ellison syndrome** A clinical syndrome defined by two physicians in 1995; they described symptoms of two patients with severe ulcer disease, massive gastric acid hypersecretion, and islet cell tumors. This term has become synonymous with the clinical features of all gastrinomas.

**zoonosis** A cycle of infection characterized by transmission between animals and humans.

**zymogen granule** The membrane-bound granules within pancreatic acinar cells that store digestive enzymes.

**zymogenic cell** One of the cell types of the gastric epithelium, found within the base; responsible for secreting enzymes needed in the chemical breakdown of food.

**zymogens** Proteolytic proenzymes that exist in cells as an inactive precursor; pancreatic zymogens are normally activated by cleavage in the gut lumen.

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